SIXTH EDITION

The American Psychiatric Association Publishing TEXTBOOK of PSYCHOPHARMACOLOGY

EDITED BY

Alan F. Schatzberg, M.D.

Charles B. Nemeroff, M.D., Ph.D.

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This Textbook is dedicated to our grandchildren-- Charlie, Brooks, Emilia, Lily, and Charlotte (AFS) and Emily, Callie, Elise, Bridget, and Logan (CBN) --who give us so much joy every day.

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Introduction

In 1996, we published the first edition of the *Textbook of Psychopharmacology*, which was generally acknowledged as an immediate success, and we are delighted that the sixth edition of *The American Psychiatric Association Publishing Textbook of Psychopharmacology* is now being published. The field has grown greatly in the past 25-plus years, with amazing advances in neuroscience, psychopharmacology, and brain stimulation therapies. Commensurate with this growth, we have with each edition tried to present the most salient information both from basic neuroscience as it relates to the pathogenesis and pathophysiology underlying psychiatric disorders and from basic and clinical psychopharmacology. Each successive edition has understandably become larger as we have attempted to keep pace with the ever-growing body of knowledge in the field. The *Textbook* now has more than 160 authors--including more than 75 new contributors. It has 12 all-new chapters, and it is fully aligned with the revised DSM-5-TR classification. This Sixth Edition is published in two volumes.

The opening section in Volume 1--Principles of Neuropsychopharmacology--contains 9 chapters and provides a tour of the multiple disciplines that undergird the chapters to come, with topics extending from the principles of molecular biology and genomics to the rudiments of neuroimaging and personalized medicine in psychiatry. The second section--Classes of Psychiatric Treatments--contains 38 chapters and provides a comprehensive examination of the medication classes used in psychopharmacological treatment as well as the available neuromodulation therapies. For each drug within a class, data are reviewed on history and discovery, preclinical and clinical pharmacology, pharmacokinetic parameters, mechanism of action, indications and efficacy, side effects and toxicology, and drug-drug interactions. Similar data are provided for brain stimulation modalities. A detailed Index closes this volume.

Volume 2 of the *Textbook* contains the third and final section--Psychopharmacological Treatment--and consists of 20 chapters focused on psychopharmacological approaches to treatment of patients with major psychiatric disorders (e.g., mood and anxiety disorders, schizophrenia, substance use disorders) as well as patients in specific populations (e.g., adults with ADHD, pediatric patients). For each specific condition, patient population, or setting, chapters provide guidance on topics such as medication selection, combination and maintenance dosing regimens, side-effect monitoring and management, and optimization of treatment response. Following these chapters is an Appendix of Psychiatric Medications, with key information on each of the agents covered in the *Textbook*, presented in a convenient tabular format. A detailed Index closes this volume.

Noteworthy additions to this *Textbook* include chapters addressing the following topics:

- Potential roles of personalized medicine in psychiatry and of artificial intelligence and machine learning in psychopharmacology
- New medications with novel pharmacological mechanisms, including ketamine and esketamine, the neurosteroid antidepressant brexanolone, and the atypical antipsychotic pimavanserin
- Use of investigational agents, such as psychedelics, in psychiatric treatment
- Treatment of alcohol use disorder, PTSD, OCD, and autism spectrum disorder
- Treatment of ADHD in adults
- Treatment of women in all life phases, including during pregnancy and the postpartum period
- Treatment of individuals with intellectual developmental disorder

With a level of detail not found in any other source, our new edition of *The American Psychiatric Association Publishing Textbook of Psychopharmacology* illuminates the path to effective evidence-based practice of psychopharmacology for novice and seasoned clinicians alike. We hope you will share our great enthusiasm for this Sixth Edition of the *Textbook of Psychopharmacology*.

This *Textbook* would not have been possible without the superb work of our managing editors, Adrienne Bronfeld and Kelly Puzdrak, who coordinated the efforts and time lines of the chapter authors. In addition, we wish to thank John McDuffie, who recently retired from his position as Publisher of American Psychiatric Association Publishing, for his support of this and previous editions. Greg Kuny, Managing Editor for Books, who also retired recently, has been steadfast in his editing and handling of the details of manuscript preparation. We are fortunate that his successor, Jennifer Gilbreath, has taken on this role for the Sixth Edition *Textbook*. We also are appreciative of the efforts of Rebecca Richters (Senior Editor, Books), Tammy Cordova (Senior Graphic Design Manager), Judy Castagna (Assistant Director of Production Services), and Erika Parker (Acquisitions Editor), Annie Birge (Acquisitions Coordinator), Christie Couture (Associate Director, Marketing), and Margaret May (Marketing Associate) on this and other textbooks we have edited. Robert B. MacArthur, Pharm.D., has provided superb editorial assistance in ensuring accurate information regarding formulations and dosages of all available medications. Finally, Saul Levin, Medical Director of the American Psychiatric Association, and Laura Roberts, Editor-in-Chief, have our eternal gratitude for their support on this project.

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PART I

Principles of Pharmacology

CHAPTER 1

Basic Principles of Molecular Biology and Genomics

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In the early years of the twenty-first century, corporate and government-funded efforts succeeded in the initial sequencing of the human genome (Lander *et al.* 2001; Venter *et al.* 2001). This landmark achievement facilitated a "genetic revolution" that has seen rapid advances in the biomedical sciences. In only two decades, genome-wide profiling technologies have provided unprecedented insights into basic biological mechanisms and disease states. Much new knowledge is generated continuously by in-depth studies of the human and a plethora of other genomes ranging from worms to primates. Notably, because classic protein-coding genes account for only 1%-2% of the human genome, many investigators have devoted their attention to the remaining "dark matter," with surprising new findings pertaining to regulation of gene expression.

Curation of genome-and transcriptome-wide profiling data has produced several publicly available biological repositories such as The Encyclopedia of DNA elements (ENCODE), Entrez Gene, Ensembl, GENCODE, and FANTOM. While fewer protein-coding genes than initially predicted have been identified, genome annotation efforts have uncovered a vast quantity of non-protein-coding genes that contribute to complex gene regulation networks. Further complexity derives from the observation that genes can have transient roles during embryogenesis or functionalities that are specific to a particular tissue or cell type. Despite rapid progress, further elucidation of

gene function and regulation in the developing and adult human brain is necessary to decipher the etiology of psychiatric conditions.

Early studies provided a rudimentary understanding of psychiatric genomics using chromosomal linkage to map putative disease risk genes. High-resolution, single-nucleotide sequencing technologies, in combination with sophisticated bioinformatic tools, have permitted the identification of specific gene variations associated with psychiatric diseases. A growing catalog of genomic aberrations, including insertions, deletions (indels), copy number variations (CNVs), and single nucleotide polymorphisms (SNPs), has shed light on disease processes. These rapid advances in genomics are contemporaneous with the advent of myriad cellular and molecular biology tools, including cellular reprogramming, epigenetic profiling, RNA inhibition, gene transfer, genome editing, chemogenetics, and optogenetics, to name a few. With this tremendous suite of capabilities, researchers are making rapid discoveries that are increasing our collective understanding of biochemical defects and guiding possible new approaches toward ameliorating those defects.

In this chapter, we present information about genetics, genomics, and the genome, as well as providing an overview of modern molecular biology and the investigative methods used in that field. We also discuss pathophysiology, as related to neuropsychiatry and molecular strategy, and introduce findings from studies on the cell biology of the neuron that help us to understand both psychopharmacology and the biology of the brain and mind. Remarkable progress that has transpired since the publication of the previous edition of this book includes an increased appreciation of epigenetic mechanisms in psychiatric disease, broad implementation of genome editing technologies, and increasingly sophisticated tools to control neural activity. FDA approval has now been granted for several viral vector and antisense oligonucleotide therapies for neurological conditions, providing proof of concept for psychiatric disorders. We discuss some of these advances in this chapter, but we caution readers that keeping pace with rapid developments requires continuous observation of relevant literature.

Cell Biology of Neurons and Glia

Neurons are specialized cells that function to transmit signals to other neurons, muscles, and secretory cells. Neurons contain four basic domains (Figure 1-1) that serve to receive signals, process and integrate signals, conduct impulses, and transmit signals.

The nucleus resides in the cell body (the signal processing domain) and contains DNA encoding genes that are expressed by neurons. Activation of a given protein-coding gene results in the generation of a messenger RNA (mRNA) that is subsequently translated into a protein (see below). Although these processes are common to all cells, neural cells are unique in some aspects of molecular signaling. Notably, the variety of genes expressed is far greater in the brain than in any other organ or tissue. It has been estimated that in aggregate, the brain expresses up to 10 times the number of genes expressed in any other tissue. This suggests an extraordinary heterogeneity of gene expression among neurons and glia that allows for a rich regulation when they assemble into the elaborate network of the human brain. Furthermore, neurons are highly specialized, metabolically active cells with robust transcriptional

outputs that are dynamically regulated in response to complex homeostatic fluctuations including neuronal activity.

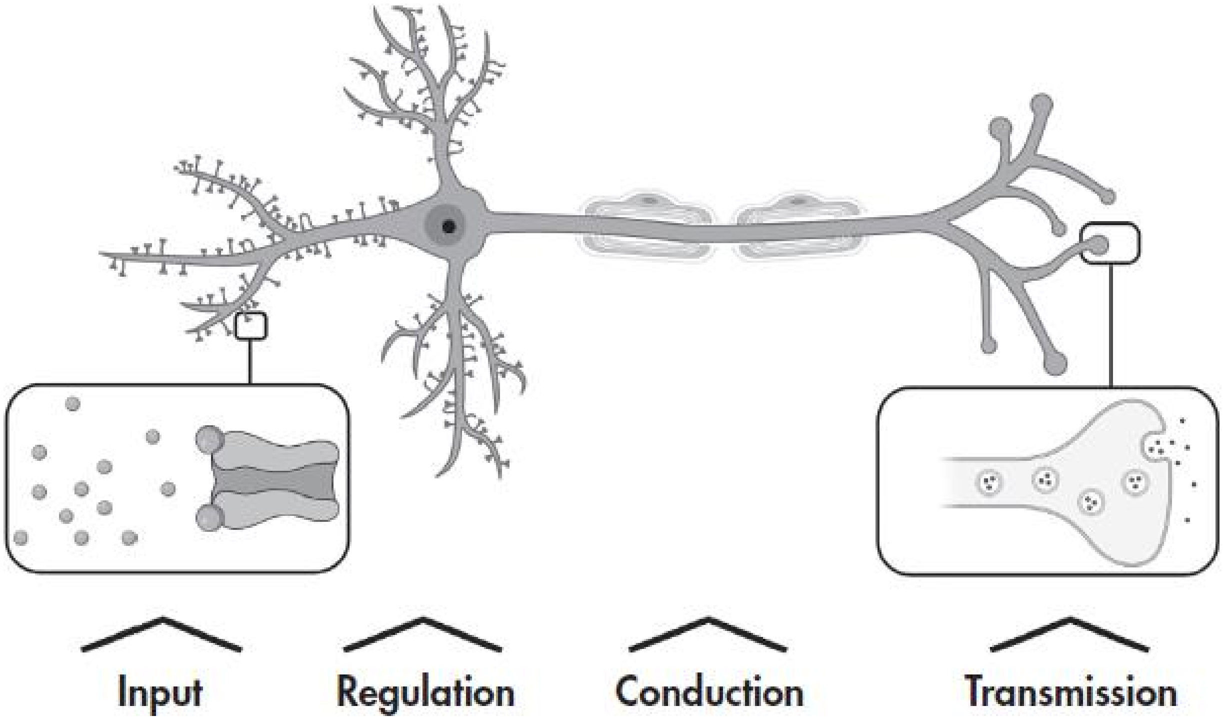

FIGURE 1-1. Diagram of a typical neuron.

As described in the text, this neuron is divided into zones for reception of signals (input = dendrites), integration of signals (regulation = nucleus and soma), conduction of signals (axon), and transmission of signals (axon terminal).

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mRNA molecules exported from the nucleus are translated into proteins by ribosomes in the endoplasmic reticulum. Most of the protein production occurs in the cell body, although some mRNA reside at dendrites and are translated locally in response to synaptic activity (Steward and Wallace 1995). Proteins destined for axon termini must be transported from the cell body, a distance that can be as great as 1 meter. These proteins are often packaged in vesicles, and specialized "motor" molecules transport packaged proteins down microtubule "tracks" at the cost of adenosine triphosphate (ATP) hydrolysis (Setou *et al.* 2000).

Essential Principles of Gene Expression

Genes and DNA

The DNA double helix transmits genetic information from generation to generation and is the repository of information required to guide an organism's development and interaction with the environment. The role of DNA in storing and transferring hereditary information depends on the innate properties of its four constituent bases: the two purine bases, adenine (A) and guanine (G), and the two pyrimidine bases, cytosine (C) and thymine (T). Within the DNA double helix, A is complementary to T, and G is complementary to C. Each block of DNA that codes for a single RNA or protein is called a *gene*, and the entire set of genes in a cell, organelle, or virus forms its *genome*. Cells and organelles may contain more than one copy of their genome. When "unraveled," the total DNA of a single human cell is approximately 2 meters in length. This large amount of genetic material is efficiently packed into the cell nucleus, which is also the site of DNA replication and transcription. Only a small percentage of chromosomal DNA in the human genome is composed of protein-coding genes, but modifications such as alternative splicing and RNA editing increase the complexity and number of proteins that are produced from RNA templates.

Importantly, many cellular RNA species (small or long) are noncoding in the sense that they do not have any open reading frame and cannot code for protein synthesis. Every cell contains a dizzying array of RNA species, many of which have been desultorily studied to date. Ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), microRNA (miRNA), and long noncoding RNA (lncRNA), as well as other RNA species, have independent cellular functions. The most abundant long cellular RNA, mRNA, serves as a template for protein synthesis. RNA, like DNA, is composed of four nucleotide building blocks. However, in RNA, the nucleotide uracil (U) takes the place of thymine (T), and RNA is a flexible single strand that is free to fold into a variety of conformations. Thus, the functional versatility of RNA greatly exceeds that of DNA.

Chromosomal DNA contains both genes and more extensive intergenic regions. Some regions of DNA in genes act as the template for RNA, but some regions are responsible for regulatory functions. The distribution of genes on chromosomes is not uniform; some chromosomal regions, and indeed whole chromosomes, are richly endowed with genes, whereas other regions are more amply supplied with noncoding DNA (although some nongenomic DNA codes for miRNA). Regulation of gene expression conferred by the nucleotide sequence of a DNA molecule is referred to as *cis*-regulation, because the regulatory and transcribed regions occur on the same DNA molecule. *Cis*-Regulatory elements that determine the transcription start site of a gene are called *basal* (or *core*) *promoters*; other *cis*-regulatory elements are responsible for tethering different activators and repressor proteins to DNA. There are specific regions of DNA that bind to regulatory proteins. These regulatory proteins may be encoded at any region in the genome, and because they are not coded by the stretch of DNA to which they bind, they are sometimes called *trans*-acting factors. *Trans*-acting factors that regulate the transcription of DNA are also called *transcription factors*.

DNA Replication

Chromosomal DNA must be replicated to coordinate with cell division. Replication begins at a sequence called the *origin of replication*. It involves the separation of the double-helix DNA strands over a short length and the binding of enzymes, including DNA and RNA polymerases. During DNA replication, each existing strand of DNA serves as a template for the synthesis of a new double helix that contains one old strand and one strand that is newly synthesized but complementary. This process is known as *semiconservative replication*. In the process of cell division, each of the 46 double helices is replicated and folded into chromosomes.

Transcription

Only a fraction of all the genes in a genome are expressed in a given cell or at a given time. These genes undergo the process of *transcription*, in which an RNA molecule complementary to one of the gene's DNA strands is synthesized in a 5' to 3' direction, using nucleotide triphosphates. Transcription can be divided into three discrete steps: initiation, mRNA chain elongation, and chain termination. Transcriptional regulation may occur at any step in the process; however, initiation appears to be the primary control point because, in a sense, it is the rate-limiting step. Localization of the transcription start site and regulation of the rate of transcription are essential to initiation. The *cis*- and *trans*-acting factors described earlier in this section all regulate the initiation of transcription.

Translation

Each mRNA in a cell can code for the primary amino acid sequence of a protein, using a triplet of nucleotides (*codon*) to represent each of the amino acids. Some amino acids are represented by more than one codon, because there are more triplet codons than there are amino acids. The codons in mRNA do not interact directly with the amino acids they specify. The translation of the individual codons of mRNA into protein depends on the presence of another RNA molecule, tRNA, which has a cloverleaf structure. On the top leaf of the tRNA structure, three nucleotides form a complementary codon, an *anticodon*, to each mRNA nucleotide triplet. Thus, each mRNA nucleotide triplet can code for a specific amino acid. Each tRNA carries an amino acid corresponding to its anticodon, and when thus "charged," the complex is termed *aminoacyl-tRNA*. Anticodons of aminoacyl-tRNA bind with mRNA codons in ribosomes. Ribosomes, a complex of rRNA and enzymes needed for translation, provide the structure on which tRNA can bind with the codons of mRNA in sequential order.

Initiation of protein synthesis involves the assembly of the components of the translation system. These components include the two ribosomal subunits, the mRNA to be translated, the aminoacyl-tRNA specified by the first codon in the message, guanosine triphosphate (GTP), and initiation factors that facilitate the assembly of this initiation complex. In eukaryotes, there are at least 12 distinct translation initiation factors (Roll-Mecak *et al.* 2000). After the ribosome recognizes the specific start site on the mRNA sequence, which is always the codon AUG coding for methionine, it slides along the mRNA molecule strand and translates the nucleotide sequence one codon at a time, adding amino acids to the growing end of the polypeptide chain (the elongation process). During elongation, the ribosome moves from the 5' end to the 3' end of the mRNA that is being translated. The binding of GTP to the elongation factor Tu (EFTu) promotes the binding of aminoacyl-tRNA to the ribosome (Wieden *et al.* 2002). When the ribosome finds a stop codon (UAA, UGA, or UAG) in the mRNA, the tRNA and the newly synthesized protein are released from ribosomes with the help of release factors that also bind GTP. The translation process is stopped, and a nascent protein exists.

Regulation of Gene Expression

Chromatin and DNA Methylation

Biophysics and molecular biology have revealed that chromatin consists of a repetitive nucleoprotein complex, the nucleosome. This particle comprises a histone octamer, with two copies of each of the histones H2A, H2B, H3, and H4, wrapped by 147 base pairs of DNA. In the octamer, histones H3 and H4 are assembled in a tetramer, which is flanked by two H2A-H2B dimers. A variable length of DNA completes the second turn around the histone octamer and interacts with a fifth histone, H1. H2A, H2B, H3, and H4 are variously modified at their amino-and carboxyl-terminal tails to influence the dynamics of chromatin structure and function (Ballestar and Esteller 2002; Keshet *et al.* 1986; Kornberg and Lorch 1999; Strahl and Allis 2000). Although chromatin provides structure to chromosomes, it also plays a critical role in transcriptional regulation in eukaryotes because it can repress gene expression by inhibiting the ability of transcription factors to access DNA. In fact, chromatin ensures that genes are inactive until their expression is commanded. In the activation process, cells must attenuate nucleosome-mediated repression of an appropriate subset of genes by means of activator proteins that modify chromatin structure. An activator protein displaces nucleosomes, which permits a complex of proteins (general transcription factors) to bind DNA at a promoter and to recruit RNA polymerase.

Cytosine methylation at cytosine-phosphate-guanine (CpG) dinucleotides is the most common modification of the eukaryotic genome, which is catalyzed by a family of DNA methyltransferases, including Dnmt1, Dnmt3a, and Dnmt3b. CpG islands are CpG-rich regions in the genome, which are often but not always located in the promoter regions of genes and some regulatory elements (Jones 2012). Methylation of cytosines within CpG islands inhibits gene expression either by directly interfering with transcription factor binding to DNA (Ballestar and Esteller 2002) or by recruiting methyl-CpG binding domain proteins, which complex with histone deacetylase to transform chromatin to a repressive state (Ballestar and Esteller 2002; Keshet *et al.* 1986). Dnmt1 expression is remarkably high in the embryonic nervous system, consistent with the proposed role for Dnmt1 in maintaining DNA methylation in dividing neural progenitor cells (Cedar and Bergman 2009).

In addition to alterations in DNA methylation, epigenetic modifications to histone tails are thought to regulate a range of cellular functions, including transcription, replication, chromosome condensation, recombination, DNA repair, and the organization of higher-order chromatin within the nucleus (Strahl and Allis 2000). Acetylation and methylation of lysine at histone tails are the two most common histone modifications (Jenuwein and Allis 2001). Hyperacetylation of nucleosomes is strongly associated with transcription and is considered a hallmark of transcriptional activity, acting to weaken the polar interaction between the negatively charged DNA and the positively charged histone proteins and resulting in a relaxed chromatin state (Dindot *et al.* 2009; Ruthenburg *et al.* 2007). Integral components of the transcriptional machinery include histone acetyltransferase and histone deacetylase enzymes, which regulate, respectively, the addition of acetyl groups to and removal of acetyl groups from histone proteins.

The effects of histone methylation on gene function and chromatin state are mainly dependent on the specific residue that is modified. Generally, in activated gene regions, there is an enrichment of histone methylation at H3K4me, H3K36me, or H3K79me (Guenther *et al.* 2007; Heintzman *et al.* 2007; Steger *et al.* 2008). In contrast, the enrichment of histone methylation at H3K9me, H3K20me, or H4K27me is implicated in gene inactivation or silencing (Kouzarides 1999; Ruthenburg *et al.* 2007). Studies also revealed that the degree of histone methylation plays a role in gene expression activity. The trimethylation at residues of H3K9, H3K2, and H4K20 is associated with transcription repression (Barski *et al.* 2007; Mikkelsen *et al.* 2007; Vakoc *et al.* 2006). However, the mono-methylation at these residues represents the gene activation (Barski *et al.* 2007; Vakoc *et al.* 2006). These DNA modifications form the basis of epigenetics, which has taken on a prominent role in relating experience to psychiatric phenotypes (Klengel and Binder 2015).

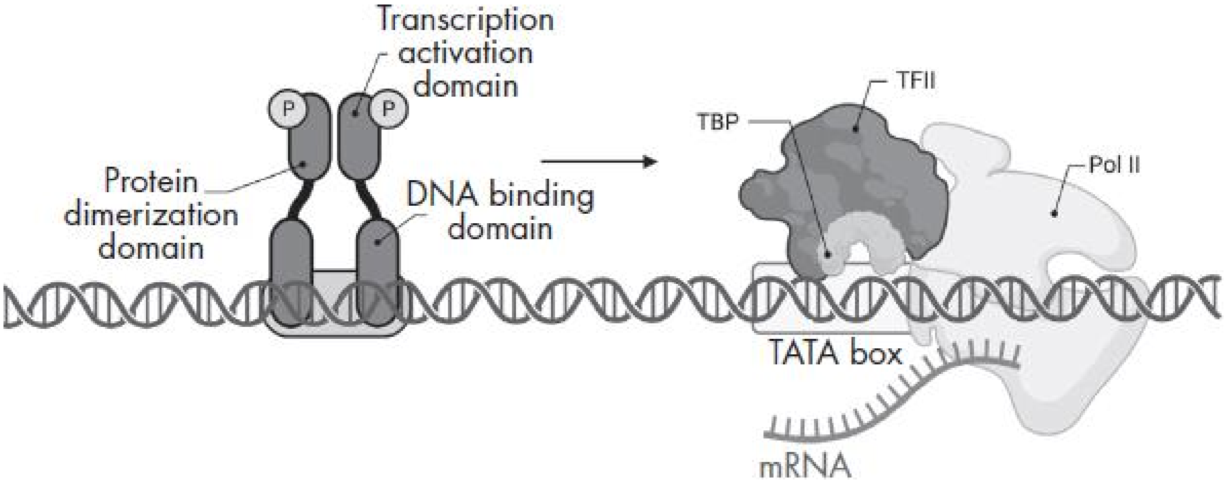

FIGURE 1-2. Transcription factors and RNA polymerase II (Pol II) complex.

Typical transcription factors contain DNA binding domains, dimerization domains, and transcription activation domains. Some transcription factors (e.g., cAMP [cyclic 3'-5'-adenosine monophosphate] response element-binding protein [CREB]) may be modified by phosphorylation. The transcription activation domain interacts with an RNA Pol II complex to induce transcription. TATA box binding protein (TBP) binds to the TATA box element and associates with general transcription factors (TFII). This gene transcription apparatus recruits Pol II to the appropriate gene. TATA box = DNA sequence rich in nucleotides A and T.

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RNA Polymerases

There are three distinct classes of RNA polymerase--RNA polymerase I (Pol I), RNA polymerase II (Pol II), and RNA polymerase III (Pol III)--in the nucleus of eukaryotic cells, and they are designed to carry out transcription. RNA Pol I synthesizes large rRNA molecules. RNA Pol II is mainly used to yield mRNA and, subsequently, proteins. RNA Pol III produces small RNA, including rRNA and tRNA molecules. Each class of RNA polymerase recognizes particular types of genes. However, RNA polymerases do not bind to DNA directly. Rather, they are recruited to DNA by other proteins that bind to promoters (Figure 1-2).

mRNA is transcribed from DNA by RNA Pol II, with heterogeneous nuclear RNA (hnRNA) as an intermediate product. The core promoter recognized by Pol II is the TATA box (Hogness box), a sequence rich in nucleotides A and T, which is usually located 25-30 bases upstream of the transcription start site. The TATA box determines the start site of transcription and orients the basal transcription complex that binds to DNA and recruits RNA Pol II to the TATA box; thus, it establishes the 5' to 3' direction in which Pol II synthesizes RNA. The formation of the basal transcription complex is promoted by a TATA box binding protein (TBP) that binds core promoters together with multiple TBP-associated factors and other general transcription factors. *Enhancers* are DNA sequences that increase the rate of initiation of transcription by RNA Pol II through its interaction with transcription factors, which can be located "upstream" or "downstream" of the transcription start site. Enhancer elements are important to cell-specific and stimulus-dependent expression of hnRNA. Some Pol II species, including those for many genes that are expressed in neurons, lack a TATA box and possess instead an *initiator*, a poorly conserved genetic promoter element.

Transcription Factors

Transcription factors act as the key regulators of gene expression. Sequence-specific transcription factors typically contain physically distinct functional domains (see Figure 1-2). Numerous transcription factors have been found. Some of them translocate to the nucleus to bind their *cis*-regulatory elements in response to their activation reaction, such as nuclear factor kB (NF-kB). However, some transcription factors are already bound to their cognate *cis*-regulatory elements in the nucleus under basal conditions and are converted into transcriptional activators by phosphorylation. cAMP (cyclic 3'-5'-adenosine monophosphate) response element-binding protein (CREB), for example, is bound to regions of DNA, called *cAMP response elements* (CREs), before cell stimulation. CREB can promote transcription when it is phosphorylated on a serine residue (ser133), because phosphorylated CREB can interact with a coactivator, CREB-binding protein (CBP), which in turn contacts and activates the basal transcription complex. Of interest, CBP possesses intrinsic histone acetyltransferase activity. The activity of most transcription factors is regulated though second-messenger pathways. CREB can be activated via phosphorylation at ser133 by second messengers such as cAMP, Ca^{++}, and growth factors (Kandel 2012) (Figure 1-3).

CREB is a molecule that is widely implicated in learning and memory in many species. Mice expressing mutant CREB isoforms show impaired memory, but this result is dependent on the genetic background of the mice (Graves *et al.* 2002). CBP is a transcriptional coactivator with CREB. A partial-knockout mouse model, in which CBP activity is lost, exhibits learning deficiencies (Oike *et al.* 1999). Furthermore, Rubinstein-Taybi syndrome (RTS) is an autosomal-dominant dysmorphic syndrome that results in severe impairment of learning and memory. The RTS gene has been mapped to chromosome 16 and identified as CBP. Loss of CBP function is likely one important contributing factor to the learning and memory defects seen in RTS (Murata *et al.* 2001; Oike *et al.* 1999; Petrij *et al.* 1995).

Posttranscriptional Modification of RNA

The mRNA of prokaryotes can be used, without any modification, to direct protein synthesis, but posttranscriptional processing of mRNA is required in eukaryotes. The DNA sequences that code for mRNA (exons) are frequently interrupted by intervening DNA sequences (introns). When a protein-coding gene is first transcribed, the hnRNA contains both exons and introns. Before the transcript exits the nucleus, its introns are removed and its exons are spliced to form mature mRNA (Figure 1-4). The hnRNA that is synthesized by RNA polymerase has a 7-methyl-guanosine "cap" added at the 5' end. The cap appears to facilitate the initiation of translation and to help stabilize the mRNA. In addition, most eukaryotic mRNAs have a chain of 40-200 adenine nucleotides attached to the 3' end. The poly(A) tail is not transcribed from DNA; rather, it is added after transcription by the nuclear enzyme poly(A) polymerase. The poly(A) tail may help stabilize the mRNA and facilitate mRNA exit from the nucleus. After the mRNA enters the cytoplasm, the poly(A) tail is gradually shortened.

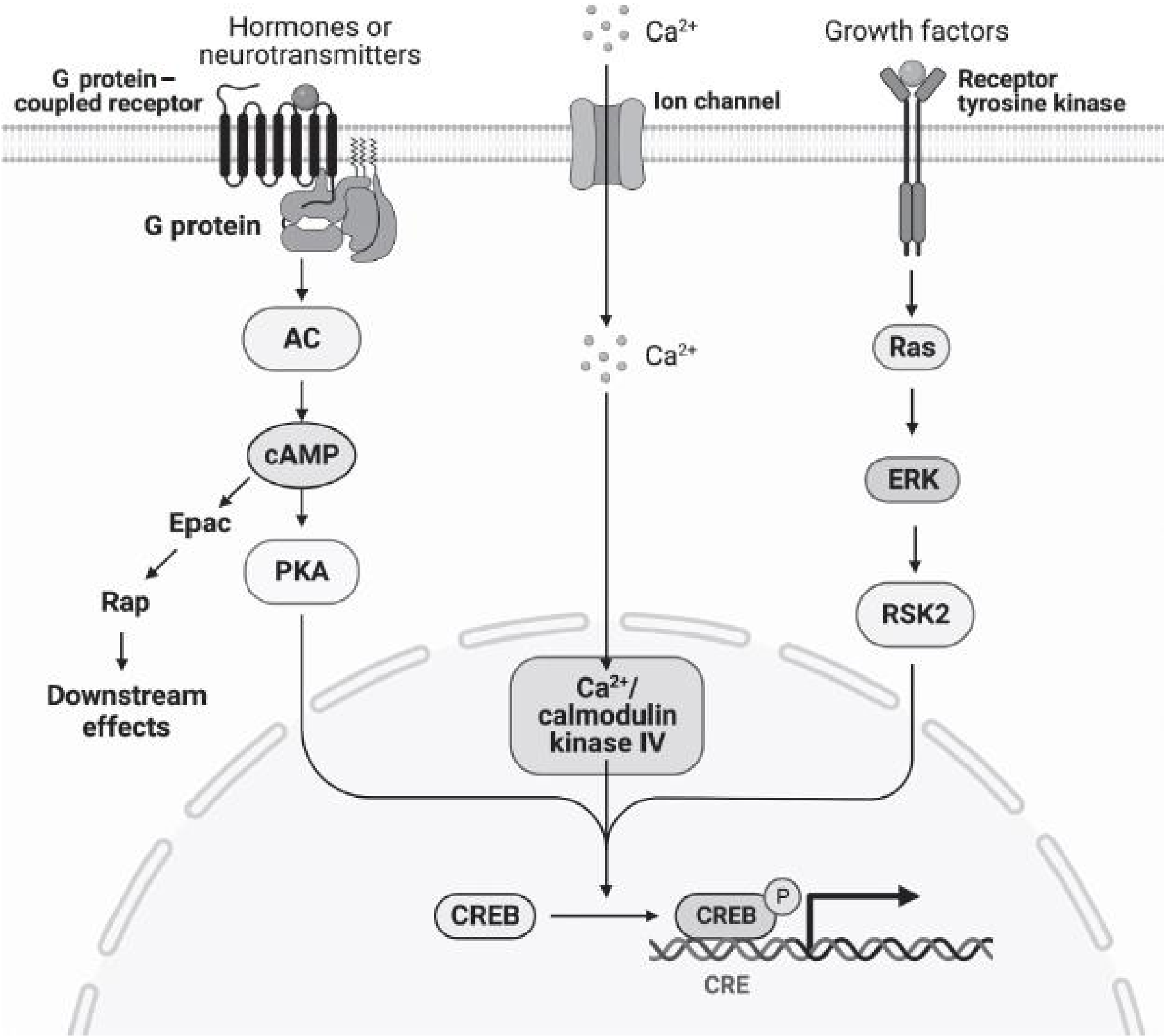
Hormones or neurotransmitters
G protein–coupled receptor
G protein
AC
cAMP
Epac
Rap
Downstream effects
PKA
Ca^{2+}
Ion channel
Ca^{2+}
Ca^{2+}/ calmodulin kinase IV
Growth factors
Receptor tyrosine kinase
Ras
ERK
RSK2
CREB
CREB
P
CRE

FIGURE 1-3. Activation of cAMP response element-binding protein (CREB) via different signal transduction pathways.

Signal cascades are activated by external stimuli, such as hormones or neurotransmitters and growth factors. *Arrows* indicate the interaction between pathways. AC = adenylyl cyclase; Ca^{2+} = calcium; cAMP = cyclic 3'-5'-adenosine monophosphate; CRE = cAMP response element; Epac = exchange protein activated by cAMP; ERK = extracellular-regulated kinase; P = phosphorylation; PKA = cAMP-dependent protein kinase; Rap and Ras = small GTPases (small proteins that bind to guanosine triphosphate [GTP]); RSK2 = ribosomal S6 kinase 2.

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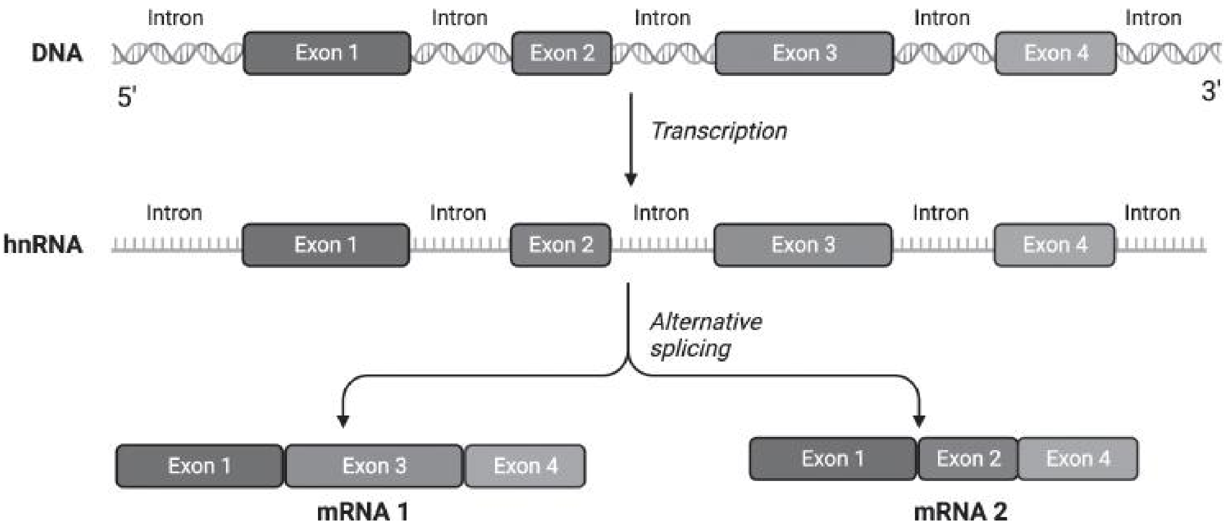
Intron
Exon 1
Intron
Exon 2
Intron
Exon 3
Intron
Exon 4
Intron
DNA
5'
3'
Transcription
Intron
Exon 1
Intron
Exon 2
Intron
Exon 3
Intron
Exon 4
Intron
hnRNA
Alternative splicing
Exon 1
Exon 3
Exon 4
mRNA 1
Exon 1
Exon 2
Exon 4
mRNA 2

FIGURE 1-4. Transcription and RNA splicing.

The *horizontal black line* between exons indicates an intron. The region before the first exon is the 5' regulatory region of the gene, such as a TATA box. There also are *cis*-regulatory elements in introns and downstream of the 3' regulatory region after the last exon. The heterogeneous nuclear RNA (hnRNA), containing both exons and introns, is spliced to form messenger RNA (mRNA). mRNAs are then exported from the nucleus to the cytoplasm, where they will direct the synthesis of distinct proteins.

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RNA Editing

RNA editing has been observed in eukaryotes ranging from protozoa to mammals and is now recognized as a type of RNA process (posttranscriptional modification of RNA) that differs from the well-known processes of RNA splicing, 5' end formation, and 3' endonucleolytic cleavage and polyadenylation (DeCerbo and Carmichael 2005; Kable *et al.* 1997). The conversion of adenosine to inosine was observed first in yeast tRNA (Grosjean *et al.* 1996) but has since been detected in viral RNA transcripts and mammalian cellular RNA (Bass 1997; Simpson and Emeson 1996). The inosine residues generated from adenosines can alter the coding information of the transcripts, because inosine is synonymous for guanosine during transcript translation. For example, upon A-to-I editing, the CAC codon for histamine is transformed to CIC, coding for arginine. RNA editing can have dramatic consequences for the expression of genetic information, and in a number of cases it has been shown to lead to the expression of proteins not only with altered amino acid sequences from those predicted from the DNA sequence but also with altered biological functions (Bass 2002; Burns *et al.* 1997).

The enzymes for RNA editing are referred to as *adenosine deaminases that act on RNA* (ADARs). ADARs target double-stranded RNA (dsRNA) and convert adenosines to inosines by catalyzing a hydrolytic deamination at the adenine base (Bass 2002). Mammals have several ADARs, of which two, ADAR1 and ADAR2, are expressed in most tissues of the body (Seeburg and Hartner 2003). RNA editing may also catalyze the conversion of a small number of adenosines in a transcript to inosines (Stuart and Panigrahi 2002). On the other hand, RNA editing can convert numerous adenosines to inosines in RNA. This type of editing is thought to be the result of aberrant production of dsRNA (DeCerbo and Carmichael 2005) and has been suggested to lead to RNA degradation (Scadden and Smith 2001), nuclear retention (Zhang and Carmichael 2001), or even gene silencing (Wang *et al.* 2005).

The serotonin 5-HT$_{2C}$ receptor is a G protein-coupled receptor that has variants generated by A-to-I editing (Burns *et al.* 1997). 5-HT$_{2C}$ receptor transcripts can be edited at up to five sites, potentially generating 24 different receptor versions and hence a diverse receptor population. The RNA-edited 5-HT$_{2C}$ receptor affects ligand affinity and the efficacy of G protein coupling (Berg *et al.* 2001; Wang *et al.* 2000; Yang *et al.* 2004). The unedited form of the 5-HT$_{2C}$ receptor has the highest affinity to serotonin and exhibits constitutive activity independent of serotonin or serotonergic agonists. When RNA is edited, the basal activity of the 5-HT$_{2C}$ receptor is suppressed and agonist potency and efficacy are modified.

Noncoding RNAs

About 2% of the human genome is transcribed into mature protein-coding RNAs, whereas the large majority, 70%-90%, is transcribed into non-protein-coding RNAs (ncRNAs). Classes of noncoding transcripts can be divided between housekeeping ncRNAs and regulatory ncRNAs.

Housekeeping ncRNAs include rRNA, tRNA, snRNA, and small nucleolar RNAs and are usually expressed constitutively. Regulatory ncRNAs can be classified into miRNAs, Piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), promoter and enhancer RNAs, and lncRNAs (Kaikkonen *et al.* 2011; Ponting *et al.* 2009). The majority of the non-protein-coding transcripts belong to the group of lncRNAs, which are arbitrarily considered as greater than 200 nucleotides in length (Ponting *et al.* 2009). However, many of these lncRNAs can also act as primary transcripts for the production of short RNAs, making the categorization of this group of ncRNAs ambiguous (Kaikkonen *et al.* 2011). The best-known ncRNAs are endogenous siRNAs. siRNAs, together with miRNAs and piRNAs, play an instrumental regulatory and defensive role in organisms. These three classes of small RNAs show overlap with regard to their structure, synthesis, and biological role. Endogenous siRNAs are involved in gene regulation and transposon silencing, although the latter mechanism is still not understood.

Modification of the Nascent Polypeptide Chain

Posttranslational modifications occur after translation is initiated. These modifications may include removal of part of the translated sequence or the covalent addition of one or more chemical groups that are required for protein activity. Some of these modifications, such as glycosylation or prenylation, represent an obligatory step in the synthesis of the "finished" protein product. In addition, many proteins may be activated or inactivated through covalent attachment of a variety of chemical groups. Phosphorylation, glycosylation, hydroxylation, and prenylation are common types of covalent alterations in posttranslational modifications. A number of different enzymes coordinate these processes, and they represent a major portion of the events of cellular signaling.

Experimental Approaches to Determining and Manipulating Gene Expression

Changes in gene expression within the CNS have profound effects for all other aspects of the organism. Changes in gene expression are causally associated not only with the development of the CNS but also with the complex phenomena of brain function, such as memory formation, learning, cognition, and affective state. Changes in gene expression may underlie the pathogenesis of many sporadic or inherited CNS-related disorders, such as Alzheimer's disease, Huntington's disease, depression, and schizophrenia. Thus, insight into and characterization of gene expression profiles are necessary steps for understanding how the brain functions at the molecular level and how malfunction will result in disease. Molecular biological and genomic technologies such as gene mapping and cloning, DNA libraries, gene transfection and expression, and gene knockout and gene targeting have provided numerous benefits to neuropsychopharmacology. Genomic methods applied to pedigree and population samples of patients with psychiatric disorders may soon make it possible to identify genes contributing to the etiology and pathogenesis of these diseases and to provide a potential basis for new therapies.

Cloning of DNA

The cloning of DNA confers the ability to replicate and amplify individual pieces of genes. Cloning can be performed with genomic DNA or complementary DNA (cDNA) that is synthesized artificially from mRNA in vitro with the aid of *reverse transcriptase*. Cloned genomic DNA may contain any stretch of DNA, either intron or exon, whereas cloned cDNA consists only of exons. For cloning (this process is outlined in Figure 1-5), the desired pieces of DNA (often called "inserts") are connected with the DNA of genetically engineered vectors or plasmids and then introduced into hosts such as bacteria or mammalian cells. A DNA library is a collection of cloned restriction fragments of the DNA of an organism that consists of random pieces of genomic DNA (i.e., genomic library) or cDNA (i.e., cDNA library). Complete cDNA libraries contain all of the mRNA molecules expressed in a certain tissue. Sometimes cDNA libraries can be from a specific tissue in a distinct circumstance. For example, a cDNA library could be made from cerebral cortex in rats with transient forebrain ischemia (Abe *et al.* 1993).

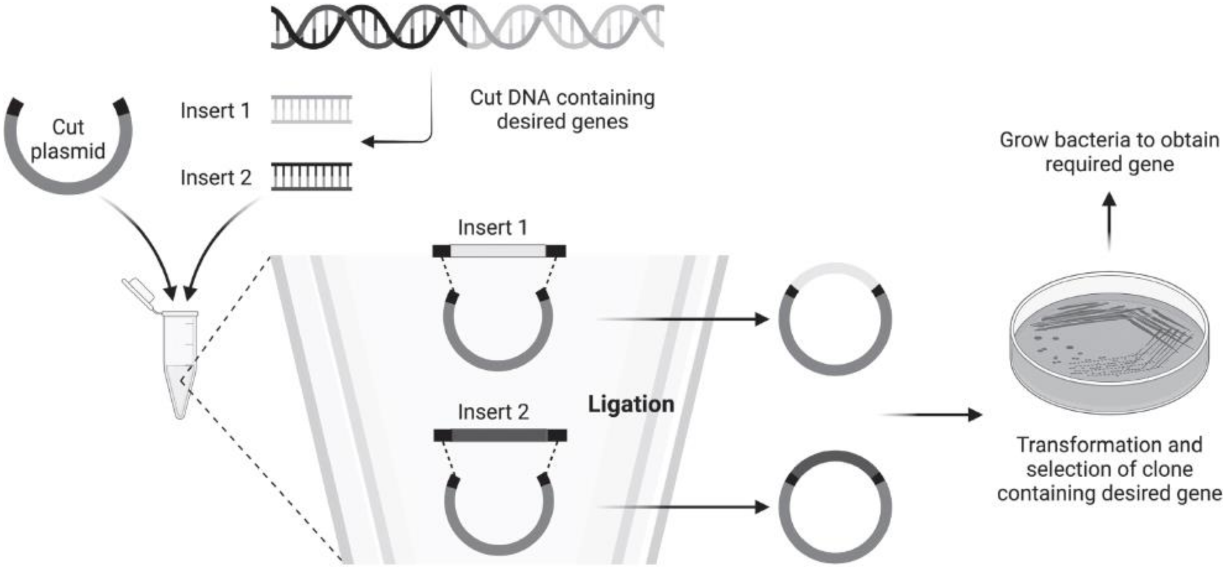

Cut plasmid
Insert 1
Insert 2
Cut DNA containing desired genes
Insert 1
Insert 2
Ligation
Grow bacteria to obtain required gene
Transformation and selection of clone containing desired gene

FIGURE 1-5. Outline of gene cloning.

See text for details.

Source. Created with BioRender.com.

The cloning of disease-related genes is an important step toward insight into the pathogenesis of diseases and development of new drugs against these diseases. If a protein is suspected of involvement in pathogenesis, a nucleic acid sequence can be deduced from the partial amino acid sequence. cDNA libraries are screened with the partial sequence in order to extract a complete clone of interest. The isolated cDNA molecules are transferred to bacteria, which amplify the cloned cDNA. Bacteria expressing these cDNA molecules will often make the protein of interest, which can be detected with antibody. A variation on the above technique uses antibodies against the purified proteins to screen a DNA library transfected into bacteriophages. The bacteriophages containing the "right" cDNA can be retrieved, and the sequence of cDNA can be analyzed.

Positional Cloning

Disease genes can sometimes be isolated with the aid of *positional cloning*, a process also known as *reverse genetics* (Collins 1995). Positional cloning is the process used to identify a disease gene based only on knowledge of its chromosomal location, without any knowledge of the gene's biological function. Positional cloning requires a genetic map of unique DNA segments or genes (genetic markers), with known chromosomal locations, that exist in several alternative forms (alleles). These allelic variations (polymorphisms) allow comparisons of the wild type as the "diseased" genotype. Linkage analysis is a method of localizing one or more genes influencing a trait to specific chromosomal regions. Genetic linkage analysis is performed by examining the cosegregation of the phenotype of interest with genetic markers. Relatives who are phenotypically alike will share common alleles at markers surrounding the genes influencing the phenotype, whereas relatives who are phenotypically dissimilar will not share these alleles. To carry out linkage analyses, investigators need, minimally, a set of families in which phenotypic individuals have known relationships to one another and the genotypes of these individuals, including one or more genetic markers.

Once the chromosomal location of the disease gene has been ascertained, the area of chromosomal DNA can be cloned. Until recently, the process of positional cloning involved laborious efforts to build a physical map and to sequence the region. (The sequencing of the human genome has obviated this step). Physical maps can be produced by isolating and linking together yeast and/or bacterial artificial chromosomes containing segments of human DNA from the region. These fragments are then sequenced and ordered, and from these data, the genomic DNA sequence for the region of the candidate gene is determined.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) is a rapid procedure for in vitro enzymatic amplification of specific segments of DNA. Amplification of the genes of interest involves selecting and synthesizing "primers"--stretches of DNA that span the region of interest to be "filled in"--and heating DNA to "melt" into single-stranded DNA, allowing polymerase and primers to bind. The polymerase then reads the "blank" stretch of DNA between the primers and synthesizes DNA corresponding to the region of interest. PCR is usually performed in thermal cyclers that heat the DNA at regular intervals and allow "cycles" of PCR to amplify the genes repetitively. To avoid continual addition of polymerase, laboratories use DNA polymerase from bacteria that inhabit hot springs or hot ocean vents. These polymerases are resistant to denaturing by heat and can therefore support several cycles of PCR.

A variation on PCR is *reverse transcriptase PCR* (RT-PCR), in which the RNA is the template. Retroviral reverse transcriptase is employed to synthesize cDNA from RNA. Enzymatic amplification of this cDNA is then accomplished using PCR. Traditional PCR is an end-point method, whereas real-time PCR is more quantitative because of detection chemistries that report the presence of PCR products after each round of amplification. PCR chemistries consist of fluorescent probes including DNA-binding dyes (ethidium bromide or SYBR Green I), hydrolysis probes (5'-nuclease probes), and hybridization probes (Valasek and Repa 2005). Each type of probe has its own unique characteristics, but the strategy for each is to link a change in fluorescence to amplification of DNA (Kubista *et al.* 2006). The instrumentation to detect the production of PCR must be able to input energy for excitation of fluorescent chemistries at the desired wavelength and simultaneously detect a particular emission wavelength. Many instrument platforms are available for real-time PCR.

Next-Generation Sequencing

The quantification of RNA using real-time RT-PCR is a routine method of assessing gene expression. However, important limitations are the small number of genes that can be assayed in one experiment and potential artifacts due to PCR amplification. Alternative, hybridization-based technologies such as microarray and NanoString use fluorescent probes that are complementary to known target sequences and attached to a solid substrate. After hybridization with samples, microscopic imaging of the substrate is then used to compute transcription rates for many genes simultaneously. Although there are instances where these technologies are advantageous, they have largely been replaced by the preeminent technology for profiling global RNA expression, massively parallel "next generation" RNA sequencing.

Reagents and instruments for RNA sequencing sold by Illumina, Inc., have been broadly adopted across academic, clinical research, biotechnology, and pharmaceutical sectors. Illumina sequencing technology involves four steps: sample preparation, cluster generation, sequencing by synthesis, and data analysis. Sample preparation involves ligation of adapter sequences to the 5' and 3' ends of fragmented template DNA or cDNA reverse transcribed from RNA. Template DNA is then amplified by PCR using primers complementary to the adapter sequences. During this process, additional sequences are added to ends of DNA amplicons to allow for sequence indexing and attachment of fragments to a solid substrate called a flow cell. The flow cell is a glass slide with lanes that contain a "lawn" of oligonucleotides complementary to adapter sequences of DNA templates. Adapter-ligated DNA is hybridized to oligonucleotides on the flow cell and clonally amplified to produce millions of "clusters" that represent the template sequences in discrete physical space on the flow cell. Detection of cluster sequences relies on their synthesis using fluorescently labeled nucleotides, each having a unique emission wavelength. As nucleotides are incorporated into the new DNA strand according to the sequence of template DNA, the sequence is inferred from the emission of light from newly incorporated nucleotides. The emission wavelength and intensity are measured in a massively parallel process for hundreds of millions of clusters on the flow cell. Billions of sequencing "reads" of 100 to 150 base pairs are produced in single or paired-end workflows, representing all the template fragments from a given sample. Sequencing reads are bioinformatically assembled into a contiguous sequence and aligned to the reference genome. Although the Illumina platform has dominated the industry, alternative technologies such as Ion Torrent and Nanopore sequencing are among their competitors.

Because of the large size of mammalian genomes, achieving sufficient read depth across the entire genome can be cost prohibitive. Therefore, as an alternative to whole-genome sequencing, whole-exome sequencing may be used, wherein only the protein-coding regions of the genome are sequenced. Once data are generated and analyzed, associations between phenotypes and genetic variations within a population may be assessed using various study designs, including genome-wide association studies (GWAS). Differential gene expression can be assessed by RNA sequencing, wherein the number of reads that are mapped to a given gene (read count) is used to infer gene expression levels.

A major limitation of most gene expression studies is the use of bulk RNA preparations from complex tissues containing multiple cell types. In response to this, single-cell RNA sequencing (scRNA-seq) is rapidly gaining popularity because of the ability to obtain high-resolution, cell-type-specific gene expression data from heterogeneous tissues like the CNS. However, the complex architecture of the adult brain and elaborate neuronal morphologies make it resistant to dissociation into intact single-cell preparations suitable for scRNA-seq. Therefore, cellular nuclei isolated from brain tissues are typically used for scRNA-seq studies. Notably, cellular nuclei are structurally resilient, enabling single-nuclei RNA sequencing to be carried out on frozen brain tissues. Assessing transcriptional landscapes at single-cell resolution is particularly important for the neurosciences due to the presence of non-neuronal CNS cells such as glia, epithelial cells of the vasculature, and blood that far outnumber neurons.

Gene Delivery Into Mammalian Cells

The introduction of recombinant DNA (including desired genes) into cells is an important strategy for understanding certain gene functions in neurons or glia. Gene function studies have benefited diagnosis and therapy for a variety of disorders that affect the CNS. The delivery of desired genes into cells or brain regions provides the technological base for insight into molecular mechanisms of brain function and, ultimately, for gene therapy in the CNS.

Vectors and Delivery

For gene transfer, it is necessary to incorporate the desired cDNA into vectors, such as engineered expression plasmids or replication-deficient viruses. Vectors used for transfection generally possess two essentially independent functions: 1) carrying genes to the target cell and 2) expressing the genes properly in the target cell. In one form of transfection, *stable transfection*, cells expressing the gene of interest can be actively selected by a marker (e.g., neomycin resistance genes, *Neo*), and the cDNA or other type of foreign DNA is eventually integrated into the genome of host cells, conferring continuous expression in daughter cells. In *transient transfection*, however, foreign DNA is not integrated into the genome of cells, and thus genes of interest are only expressed for a few days.

The main barrier to the delivery of DNA into cells is getting the foreign DNA through the cellular membrane. Various chemical and physical methods have been developed to convey the foreign DNA, such as calcium phosphate coprecipitation of DNA, liposome fusion, electroporation, microinjection, ballistic injection, and viral infection. At present, methods dependent on incorporation of DNA into cationic liposomes are used most widely (e.g., lipofectin). These methods of transfection are accessible to both cell lines and cultured primary neuronal cells. Cells for hosting the foreign DNA can be either established cell lines or primary cultured neuronal cells. The desired cDNA delivered into cells may be native genes, fragments of the genes, mutant genes, or chimeric genes.

Viral Vectors

Several viral vectors with low toxicity, high transduction efficiency, and persistent expression have extended the methodology of delivery of genes to mammalian cells. These viruses include DNA viruses, such as adenoviruses and adeno-associated viruses (AAVs), herpes simplex viruses, and RNA retroviruses. As a result of advances in genetic manipulation, adenoviruses and AAVs are now more widely applied to gene transfer. The advantages of the adenoviruses are 1) the ability to carry large sequences of foreign DNA, 2) efficient transduction of a broad range of cell types 3) an almost 100% expression of the foreign genes in cells, and 4) an extremely low rate of integration into host genomes. AAV viral vectors share these attributes but have a limited payload capacity.

Human adenovirus is a large DNA virus (containing about 36 kilobase [kb] pairs) composed of early viral genes (from *E1* to *E4*) and later genes (from *L1* to *L5*). Wild-type adenovirus cannot be applied to gene transfer because it causes a lytic infection. Thus, recombinant adenoviruses with defects of some essential viral genes are used for gene delivery. These adenoviral expression systems are safe, have the capacity for large DNA inserts, and allow for relatively simple adenoviral production (Harding *et al.* 1997; He *et al.* 1998).

Meanwhile, AAV vectors have emerged as a dominant vector platform in biomedical research and clinical settings (Hastie and Samulski 2015; Wu *et al.* 2006; Xie *et al.* 2002). Clinical trials evaluating AAV vectors have shown they are well tolerated (Keeler and Flotte 2019), and effective AAV vectors have been approved for the treatment of lipoprotein lipase deficiency (Buning 2013; Yla-Herttuala 2012), Leber congenital amaurosis (Luxturna) (Dunbar *et al.* 2018), and spinal muscular atrophy (Zolgensma) (Keeler and Flotte 2019). Projections from the FDA suggest that by 2025, approximately 10 new approvals for viral vector-based drugs will be awarded annually.

All known AAV serotypes require co-infection with a helper virus to manifest productive infection. Thus, AAV is classified as a *dependovirus* that is naturally nonpathogenic. The AAV genome consists of a 4.7-kb single-stranded DNA with inverted terminal repeats (ITRs) packaged into a small non-enveloped icosahedral capsid (Wu *et al.* 2006). The short (145-base) ITRs are sufficient for vector propagation when viral *Rep* (Replication) and *Cap* (Capsid) genes are provided in trans. Therefore, with the exception of ITRs, the entire AAV genome can be replaced to accommodate a desired genetic payload.

Lentivirus belongs to the *Retroviridae* family that also includes HIV. The 8-kb lentiviral genome is a single-stranded RNA encoding several viral genes flanked by long terminal repeats. The ability of lentiviral vectors to efficiently integrate into the host genome of nonreplicating cells (including neurons) and confer stable transgene expression makes them an attractive option for gene transfer in the neurosciences. To minimize the potential for creating replication-competent vectors during production, third-generation lentiviral vector systems distribute viral genes among four different plasmids. While this practice has vastly increased the safety of lentiviral vectors, their random integration into the host genome can result in insertional mutagenesis.

Given the innate capacity of viral vectors to attach and transmit genetic material across the cell membrane, gene transfer can be achieved simply by physical interactions between viral vectors and cells. To maximize the efficiency of transduction, viral titer, the time of exposure to virus, and the multiplicity of infection should be optimized for each vector system and cell or tissue type. For in vivo studies, intracranial infusions of viral vectors into discrete brain regions result in local transgene expression, although vector titer, infusion volume, and vector selection are among critical parameters that affect dissemination, duration, cell-type specificity, and levels of transgene expression. Global transduction of the rodent brain requires infusion of viral vectors at an early postnatal time point.

Several general strategies can be employed to assess proper expression of transgenes following viral vector transduction (Chalfie *et al.* 1994; Czysz *et al.* 2015; Kohara *et al.* 2001; Yu and Rasenick 2002):

1. The measurement of functional changes elicited by gene expression in targeted cells. If an enzyme is expressed, this would involve measuring the activity of that enzyme.
2. The detection of the proteins encoded by transgenes via techniques relying on antibodies, such as western blot, immunoprecipitation, and immunocytochemistry. Expression of the desired genes tagged with some epitopes, such as hemagglutinin (HA), glutathione S-transferase

(GST), and polyhistidine tag (His-tag), can also be determined using antibodies directed against these epitopes.

3. The use of fluorescent proteins such as the green fluorescent protein as an indicator.

The improved safety and efficiency of modern viral vector systems makes them an increasingly attractive therapeutic avenue for neurological and psychiatric conditions, particularly for disorders with a known genetic etiology. Combined with emerging gene editing tools, viral vectors are likely to become an important addition to the therapeutic repertoire.

Inhibition of Cellular Gene Expression

RNA Interference

RNA interference (RNAi) is believed to be a biologically conserved function in a wide range of eukaryotic species. It may play a role in protection against dsRNA viruses (Sijen *et al.* 2001) and genome-invading transposable elements (Provost *et al.* 2002; Volpe *et al.* 2002). Triggered by dsRNA, RNAi identifies and destroys the mRNA that shares homology with the dsRNA. This natural defense mechanism can be exploited to suppress the expression of any particular gene by introducing dsRNA whose antisense strand sequence matches the mRNA sequence. The first described RNAi was in the nematode *Caenorhabditis elegans* as sequence-specific gene silencing in response to dsRNA (Fire *et al.* 1998).

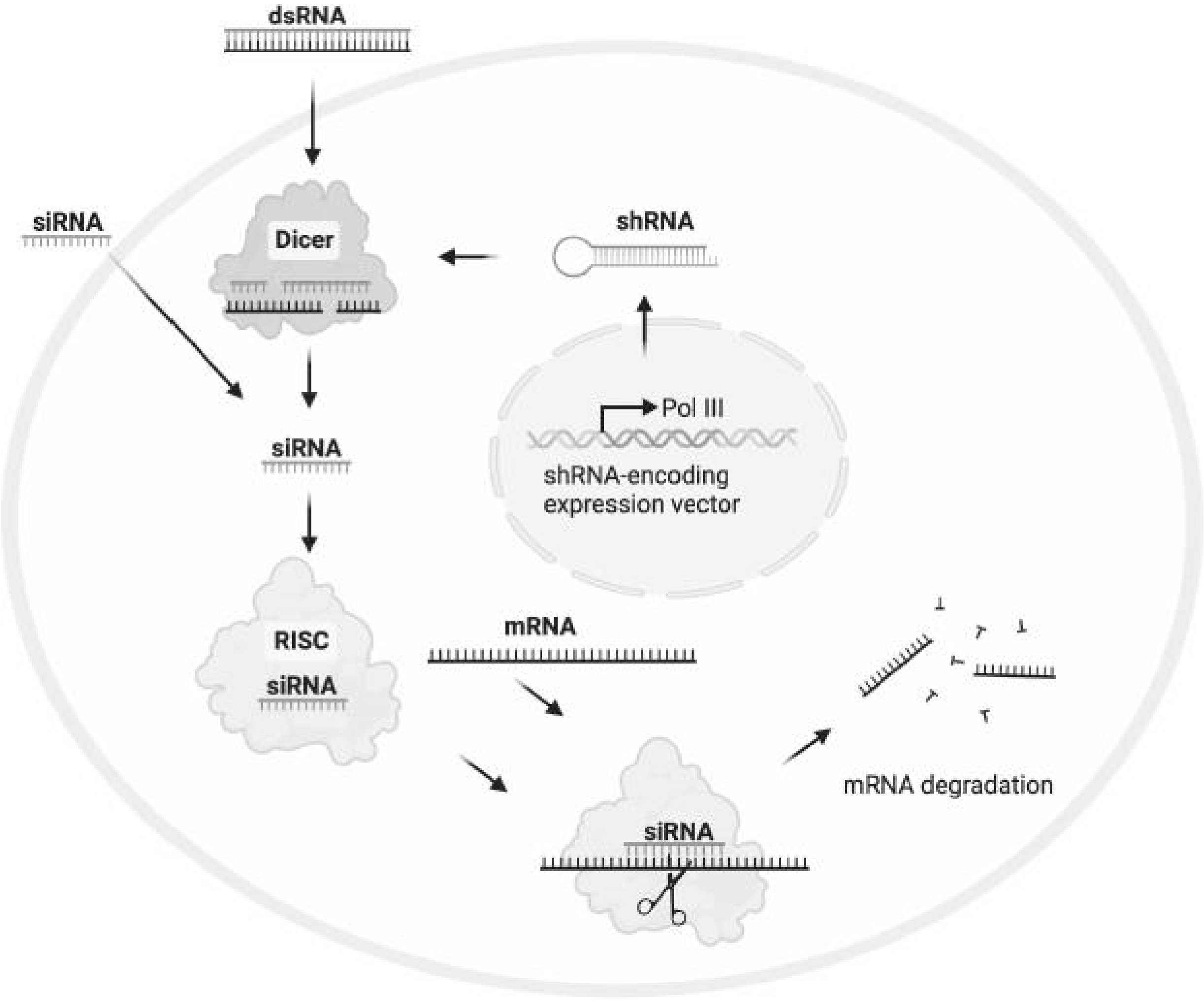

dsRNA
siRNA
Dicer
shRNA
Pol III
shRNA-encoding
expression vector
siRNA
RISC
siRNA
mRNA
mRNA degradation
siRNA

FIGURE 1-6. Schematic of the mechanism of RNA interference (RNAi) posttranscriptional knockdown of a gene product.

The procedure starts with the introduction (transfection, electroporation, or injection) of double-stranded RNA (dsRNA) or small interfering RNA (siRNA) into cells, or expression of small hairpin RNA (shRNA) in cells with vectors encoding shRNAs. The cellular ribonuclease (RNase) Dicer recognizes the long dsRNA molecules and shRNA. Subsequently, the dsRNA is cleaved, resulting in 21-nucleotide RNA duplexes, the siRNAs. These siRNA molecules are then incorporated into the RNA-induced silencing complex (RISC), where they are unwound by an adenosine triphosphate (ATP)-dependent process, transforming the complex into an active state. Activated RISC uses one strand of the RNA as a bait to bind homologous RNA molecules. The target RNA is cleaved and degraded, resulting in gene silencing. mRNA = messenger RNA; Pol III = RNA polymerase III.

Source. Created with BioRender.com.

In the initiation step, Dicer, an enzyme of the RNase III family, initiates ATP-dependent fragmentation of long dsRNA into 21-to 25-nucleotide double-stranded fragments, termed *small interfering RNAs*. These siRNAs re specifically characterized by overhanging 3' ends of two nucleotides and phosphorylated 5' ends. The siRNA duplexes bind with Dicer, which facilitates the formation of an siRNA/multiprotein complex called *RISC loading complex* (RLC). The siRNA duplex in RLC then unwinds (which requires the protein Ago2) to form an active *RNA-induced silencing complex* (RISC) that contains a single-stranded RNA (called the *guide strand*). The RISC recognizes the target RNA through Watson-Crick base pairing with the guide strand and cleaves the target RNA. Finally, the RISC releases its cleaved product and goes on to catalyze a new cycle of target recognition and cleavage (Figure 1-6) (Tomari and Zamore 2005; Xia *et al.* 2005).

miRNAs are formed in a similar manner, from longer RNA precursors, and are processed in the cytoplasm by Dicer before becoming part of a RISC. However, siRNAs are the products of exogenous dsRNAs that are taken up by cells or that enter via vectors such as viruses. siRNAs bind to mRNA in the case of complete complementarity. miRNAs are products of endogenous ncRNA encoded from genes of the genome. They do not require full complementarity to bind with target mRNA (e.g., one type of miRNA may regulate many genes, and one gene may be regulated by several miRNAs) (Carthew and Sontheimer 2009).

Antisense Oligonucleotide or RNAi Knockdown of Gene Expression

Knockdown of gene expression is accomplished by designing antisense oligonucleotide (ASO) or siRNA sequences that target the coding and noncoding regions of the specified mRNAs with perfect complementarity. In mammalian cells, administration of siRNAs is effective in short-term investigations. Introduction of ASO or siRNA into cells is accomplished by transfection or electroporation of either the specific siRNA itself or small hairpin RNA (shRNA), in which the hair loop is rapidly cleaved to produce siRNA. Most of the proposed applications of RNAi incorporate 21-nucleotide siRNA duplexes that have 2-nucleotide 3' overhangs, which allow large-scale and uniform production of siRNA molecules that can be chemically stabilized. In some siRNA-target combinations, the use of longer dsRNAs can increase the potency of RNAi (Kim *et al.* 2005; Siolas *et al.* 2005).

For stable longer-term suppression, a gene construct coding for the shRNA with a Pol III or a Pol II promoter can be applied (Brummelkamp *et al.* 2002; Shi *et al.* 2006). RNA Pol II and III promoters are used to drive expression of shRNA constructs (Amarzguioui *et al.* 2005), depending on the type of expression required. Pol III promoters drive high levels of constitutive shRNA expression, and their transcription initiation points and termination signals are well defined. Pol II promoter-driven shRNAs can be expressed tissue-specifically (Zeng *et al.* 2002). Expressed shRNAs are incorporated into a RISC, leading to a more potent inhibition of target gene expression. Generally, viral vectors such as adenovirus, lentivirus, and AAC can carry the gene construct into cells to achieve adequate and prolonged expression for knockdown (Kim and Rossi 2007).

Oligonucleotide Applications

ASOs and RNAi constitute a straightforward method for inducing sequence-specific silencing of one or more genes of interest with the introduction of ASO, siRNAs, or shRNAs. These have been powerful tools for investigating gene function in laboratory settings. Meanwhile, these same types of oligonucleotides can be used in vivo and as therapeutic agents. In the 30 years that have passed since the first studies of ASOs applied directly to the living brain (Wahlestedt *et al.* 1993a, 1993b), clinical success has been achieved in human patients, notably with the recent FDA approval of Spinraza for spinal muscular atrophy (Finkel *et al.* 2017).

Studies using RNAi have been performed in neuronal cells to examine the functional roles of individual genes in developing growth cones and neurite outgrowth (Eriksson *et al.* 2007; Hengst *et al.* 2006; Liu *et al.* 2007; Schmitz *et al.* 2007; Yanaka *et al.* 2007), ion channels (Geng *et al.* 2004;

Lauver *et al.* 2006; Tahiliani *et al.* 2007), apoptosis (Yano *et al.* 2007; Zhang *et al.* 2007), and a variety of signaling pathways (Meuer *et al.* 2007; Sanada and Tsai 2005; Shi *et al.* 2006; Yamada *et al.* 2005). Furthermore, like ASOs, RNAi can be used for the knockdown of gene expression in animals. It appears to apply in virtually all mammalian species, as exemplified by its capability for silencing genes in mice, rats, and goats (Peng *et al.* 2006; Zhou *et al.* 2007). Inducible RNAi based on the Cre-loxP system has also been developed in transgenic mice, enabling the investigator to control gene silencing both spatially and temporally (Chang *et al.* 2004; Coumoul *et al.* 2005; Peng *et al.* 2006; Xia *et al.* 2006; Zhou *et al.* 2007).

To conclude, the success of ASO and RNAi knockdown of specific genes is increasingly translated for therapeutic gene disruption in patients with genetic diseases. ASOs and RNAi have long been a frequently used tool in a wide range of biomedical research.

Chromatin Profiling Techniques

The purpose of *chromatin immunoprecipitation* (ChIP) is to identify genomic sequence(s) associated with a protein of interest (Solomon *et al.* 1988). ChIP has become the technique of choice to determine the genomic enrichment profiles of transcription factors, posttranslationally modified histones, histone variants, or chromatin-modifying enzymes. The method comprises three basic steps: 1) covalent crosslinks between proteins and DNA are formed, typically by treating cells with formaldehyde or another chemical reagent; 2) an antibody specific to the protein of interest is used to coimmunoprecipitate the protein-bound DNA fragments that were covalently crosslinked; and 3) the immunoprecipitated protein-DNA links are reversed. DNA sequences associated with the precipitated protein can be identified in various ways, including dot or slot blot, PCR, quantitative PCR, labeling and hybridization to genome-wide or tiling DNA microarrays (ChIP-chip technique) (Lee *et al.* 2006), and sequencing technology (Gogol-Doring and Chen 2012).

Optimized workflows for ChIP followed by DNA sequencing (ChIP-seq) have been commercialized and used extensively in epigenetic profiling studies, but some important limitations persist. For example, ChIP-seq is laborious, requires substantial optimization, is prone to artifact, and requires large amounts of starting material--a major limitation for analyzing small amounts of tissue or low-abundance cell types. An alternative technique gaining popularity is the *cleavage under targets and release using nuclease* (CUT&RUN), a novel chromatin mapping strategy that is less labor-intensive, provides lower background, and requires less starting material than ChIP-seq (Skene *et al.* 2018). CUT&RUN builds on Chromatin ImmunoCleavage (ChIC), wherein a fusion of protein A to Micrococcal Nuclease (pA-MNase) selectively cleaves antibody-bound chromatin in situ (Schmid *et al.* 2004). In CUT&RUN, cells or nuclei are immobilized to a solid support, with pA-MNase-cleaved DNA fragments isolated from solution. The workflow is compatible with next-generation sequencing to generate high-resolution genome-wide profiles of histone posttranslational modifications, going from cells to analyzed data in less than 1 week.

Another important technique for assessing chromatin accessibility on a genome-wide scale is the *assay for transposase-accessible chromatin using sequencing* (ATAC-seq) (Buenrostro *et al.* 2013). Whereas most epigenetic profiling approaches are specific to a given epigenetic mechanism, chromatin accessibility can be assayed by ATAC-seq without a priori knowledge of local epigenetic regulation mechanisms. In principle, ATAC-seq identifies open regions of the genome that are susceptible to DNA cleavage and tagging (tagmentation), which are catalyzed by a highly active Tn5 transposase (Buenrostro *et al.* 2015). Tagged DNA sequences are then amplified by PCR and identified using next-generation sequencing. ATAC-seq has been adopted widely as an efficient, low-input method for studying chromatin dynamics, nucleosome positioning, and transcription factor occupancy.

Genome-Editing Technologies

Genome-editing technologies based on site-specific DNA nucleases allow introduction of genetic modifications into almost any cell type and organism. To date, four major classes of customizable DNA binding proteins have been engineered for this purpose: meganucleases derived from microbial mobile genetic elements (Smith *et al.* 2006), zinc finger nucleases based on eukaryotic transcription factors (Miller *et al.* 2007; Urnov *et al.* 2005), transcription activator-like effectors from *Xanthomonas* bacteria (Christian *et al.* 2010; Miller *et al.* 2011), and the RNA-guided DNA endonuclease Cas9 (CRISPR-associated protein 9) from the type II bacterial adaptive immune system CRISPR (clustered regularly interspaced short palindromic repeats) (Cong *et al.* 2013; Mali *et al.* 2013). The most rapidly developing is the CRISPR/Cas9 system, which can be targeted to virtually any genomic location of choice via a short RNA guide. The CRISPR locus is typically composed of a clustered set of CRISPR-associated (Cas) genes and a series of repeat sequences interspaced by variable sequences (spacers) corresponding to sequences within foreign genetic elements (protospacers). A long pre-CRISPR RNA (crRNA) transcribed from the spacer-repeat CRISPR locus is processed into shorter crRNAs, which direct the nucleolytic activity of certain Cas enzymes to degrade target nucleic acids (Brouns *et al.* 2008; Hale *et al.* 2009).

Prokaryotes have evolved diverse RNA-mediated systems that use short crRNAs and Cas proteins to detect and defend against viral DNA elements (Bhaya *et al.* 2011; Marraffini and Sontheimer 2008; Wiedenheft *et al.* 2012). The guide sequence within these crRNAs can be easily replaced by a sequence of interest to retarget the Cas9 nuclease. A simple two-component system--consisting of Cas9 from the bacterial species *Streptococcus pyogenes* (Cong *et al.* 2013; Mali *et al.* 2013) or *Staphylococcus aureus* (Ran *et al.* 2015) and a fusion of the *trans*-activating crRNA-crRNA duplex to a single-guide RNA (sgRNA) (Jinek *et al.* 2012)--has been engineered for expression in eukaryotic cells and can achieve DNA cleavage at any genomic locus of interest. Hence, Cas proteins can be targeted to specific DNA sequences simply by changing the short specificity-determining part of the guide RNA (gRNA), which can be easily achieved in one cloning step (Heidenreich and Zhang 2016).

Several variants of the Cas9 nuclease have been adopted to help in genome editing. The first is wild-type Cas9, which can cleave double-stranded DNA at specific sites to form double-stranded breaks (DSBs). DSBs can be repaired by the cellular nonhomologous end joining (NHEJ) or homology-directed recombination (HDR) pathway (Burma *et al.* 2006; Kass *et al.* 2013; Maruyama *et al.* 2015). If a donor template with homology to the targeted locus is supplied, the DSB may be repaired by HDR. If an exogenous homology repair template is absent, the DSBs can be repaired by inducing insertion or deletion mutations (indels) via the NHEJ repair pathway (Bibikova *et al.* 2002). The second variant of the Cas9 nuclease is a mutant form known as Cas9D10A (Cong *et al.* 2013). It cleaves only one DNA strand and does not activate NHEJ. Instead, in the presence of a homologous repair template, DNA repairs are conducted via the HDR pathway only, resulting in reduced indel mutations (Qi *et al.* 2013). The third variant is a nuclease-deficient Cas9 (Qi *et al.* 2013). Mutations inactivate cleavage activity but do not prevent DNA binding (Jinek *et al.* 2012). Therefore, this variant can be used as either a gene silencing or a gene activation tool that "surgically" targets the desired region of the genome (Gilbert *et al.* 2013; Hu *et al.* 2014; Maeder *et al.* 2013; Perez-Pinera *et al.* 2013). It can also be applied to visualize repetitive DNA sequences with a single sgRNA or nonrepetitive locus using multiple sgRNAs fused to enhanced green fluorescent protein (Chen *et al.* 2013). Alterations of gene sequence or expression induced by the CRISPR/Cas9 system are displayed in Figure 1-7.

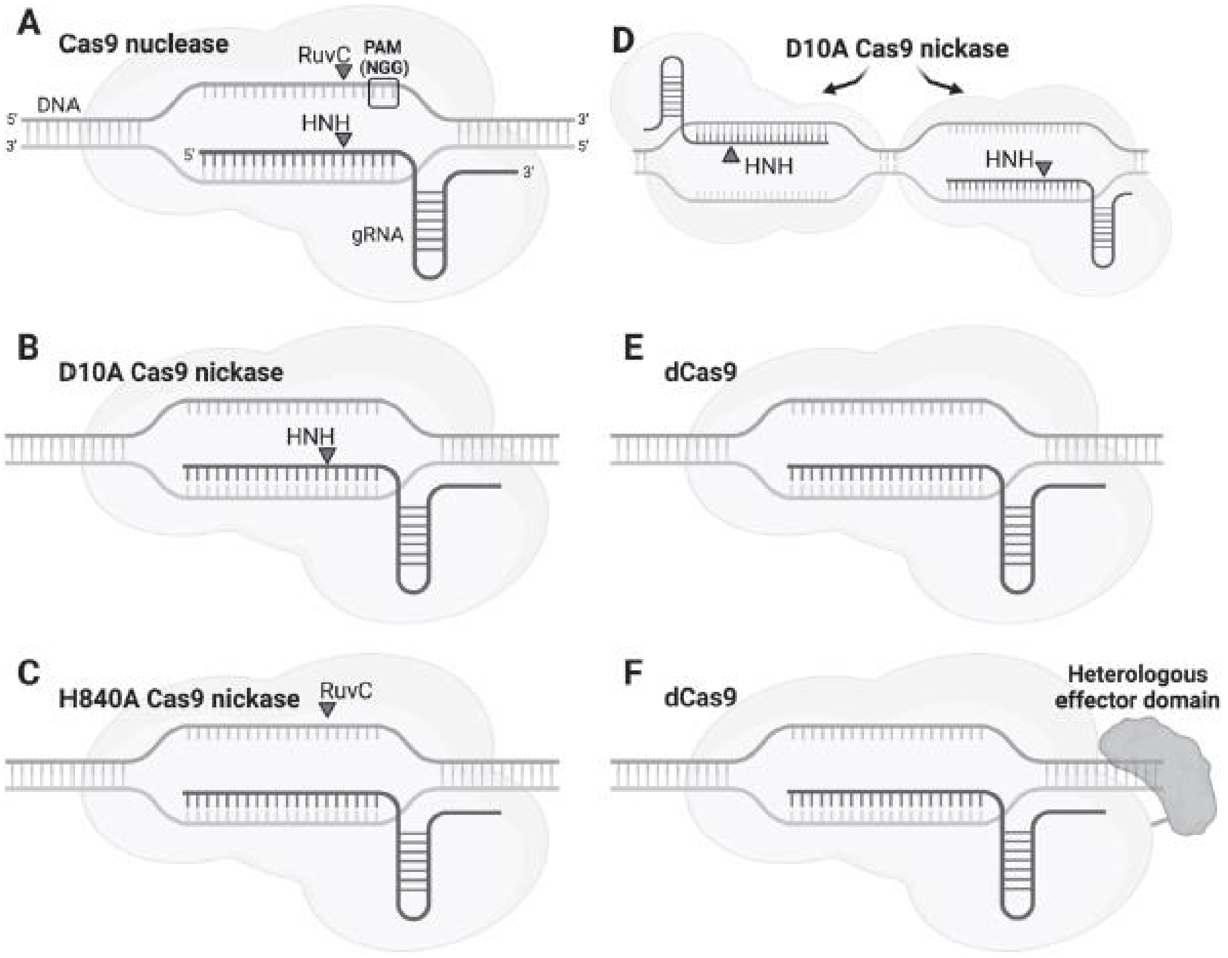

A
Cas9 nuclease
RuvC
PAM
(NGG)
DNA
5'
3'
HNH
5'
3'
3'
5'
gRNA
D
D10A Cas9 nickase
HNH
HNH
B
D10A Cas9 nickase
HNH
E
dCas9
C
H840A Cas9 nickase
RuvC
F
dCas9
Heterologous
effector domain

FIGURE 1-7. Cas9-based systems for altering gene sequence or expression.

See Plate 1 to view this figure in color.

(A) Cas9 nuclease creates double-stranded breaks at DNA target sites with complementarity to the 5' end of a gRNA. **(B)** Cas9 nickase created by mutation of the RuvC nuclease domain with a D10A mutation. This nickase cleaves only the DNA strand that is complementary to and recognized by the gRNA. **(C)** Cas9 nickase created by mutation of the HNH nuclease domain with an H840A mutation. This nickase cleaves only the DNA strand that does not interact with the small RNA. **(D)** Paired nickase strategy for improving Cas9 specificity. D10A Cas9 nickase directed by a pair of appropriately oriented gRNAs leads to induction of two nicks that, if introduced simultaneously, would be expected to generate a 5' overhang. **(E)** Catalytically inactive or "dead" Cas9 (dCas9) that can be recruited by a gRNA without cleaving the target DNA site. **(F)** Catalytically inactive dCas9-bearing dual D10A/H840A mutations fused to a heterologous effector domain. Cas9 = CRISPR-associated protein 9 nuclease from *Streptococcus pyogenes*; CRISPR = clustered regularly interspaced short palindromic repeat; gRNA = guide RNA; PAM (NGG) = protospacer adjacent motif (sequence 5'-NGG-3', where "N" is any nucleobase followed by two guanine ["G"] nucleobases).

Source. Created with BioRender.com.

The CRISPR/Cas9 system has achieved widespread use in targeting genes in many cell lines and organisms, including humans (Mali *et al.* 2013), bacteria (Fabre *et al.* 2014), zebrafish (Gonzales and Yeh 2014), *C. elegans* (Hai *et al.* 2014), plants (Mali *et al.* 2013), frogs (Bhattacharya *et al.* 2015), yeast (Jacobs *et al.* 2014), flies (Li and Scott 2016), monkeys (Chen *et al.* 2015), rabbits (Yan *et al.* 2014), pigs (Hai *et al.* 2014), rats (Bao *et al.* 2015), and mice (Kalebic *et al.* 2016). In neuroscience research, the benefits of using CRISPR/Cas9 systems to study the nervous system are highlighted by several successful applications studying synaptic and circuit function, neuronal development, and diseases (Heidenreich and Zhang 2016). The delivery of Cas9 and sgRNA to target the methyl CpG binding protein 2 gene *Mecp2* in the adult mouse brain demonstrated phenotypes observed in classic *Mecp2*-mutant mouse models and patients with Rett syndrome (Swiech *et al.* 2015). Cas9-mediated deletion of common tumor-suppressor genes in the cerebellum and forebrain efficiently induced the formation of medulloblastoma and glioblastoma tumors, respectively (Zuckermann *et al.* 2015). Although NHEJ in postmitotic neurons has been demonstrated to be active, introduction of precise genetic mutations via HDR in the brain may remain challenging. It is commonly believed that HDR predominantly occurs in the S (synthesis) and G_2 (gap between DNA synthesis and mitosis) phases of the cell cycle, and HDR is therefore thought to be rare in nondividing cells, such as neurons (Heidenreich and Zhang 2016).

Transgenic and Gene-Targeting Techniques

Over the past few decades, progress in the development of molecular genetic methods has enabled the manipulation of genes in intact organisms, such as mice. The technologies have provided a powerful and useful tool that allows the study of gene function and promotes understanding of the molecular mechanisms of disorders of the brain and mind. The mouse genome is by far the most accessible mammalian genome for manipulation. Many successful procedures for introducing new genes, expressing elevated levels of genes, and eliminating or altering the function of identified target genes have been reported. Many mouse models produced by manipulating genes may be used in a variety of fields relevant to neuroscience. It is noteworthy, however, that behavioral studies in mice differ from those in rats, let alone primates, and several factors induce variability. As a result, interpretation of genetically induced behavioral alterations must be made with caution (Richter *et al.* 2009).

Generally, transgenic mice are those that express exogenous DNA because of the insertion of a gene into the mouse genome. Usually, that gene is randomly located within the mouse genome, often as several copies. The use of transgenic mice has represented a major strategy for the investigation of genetic questions following research establishing the feasibility and reproducibility of stably introducing DNA by microinjection into individual male mouse embryos (Markert 1983). In DNA constructs used for the generation of transgenic mice, the gene of interest is located 3' to promoter sequences to produce a desired distribution of gene expression. Selection of the promoter is the most important consideration in generating transgenic mice. Some promoters, such as platelet-derived growth factor (PDGF), thy1 (a cell surface glycosylphosphatidylinositol-linked glycoprotein), prin (PrP), neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP), have demonstrated the ability to direct high-level expression of exogenous genes in brain and/or in the neurons of mice (Hsiao *et al.* 1996; Nolte *et al.* 2001; Sturchler-Pierrat *et al.* 1997; Yang *et al.* 2004; Zhu *et al.* 2001). This level of expression can be modified by incorporation of a "tet-on" or "tet-off" vector into the desired inserted gene. Depending on the nature of the switch (on or off), the mouse will express the gene of interest when ingesting (or taken off) doxycycline.

Gene targeting refers to the homologous recombination that occurs between a specifically designed targeting construct and the chromosomal target of interest, in which recombination at the target locus leads to replacement of the native target sequence with a construct sequence. The method enables the precise introduction of a mutant into one of many murine genes and has proven invaluable in examining the roles of gene functions in complex biological processes. Most of the target constructs are used to disrupt a target and to eliminate gene function (conventional "knockout"). Generally, a gene-targeting construct that contains positive-negative selection markers is prepared such that the target gene is interrupted by the gene for neomycin resistance, which also serves as a positive selection marker, and a thymidine kinase (TK) gene is adjacent to either one or both ends of the homologous genomic sequence for negative selection (Gusella *et al.* 1983). The positive-negative deletion scheme is employed to enrich for homologous recombination.

The targeting construct is often introduced into mouse embryonic stem cells by electroporation. Cells that fail to integrate the targeting construct into the genome are killed by application of neomycin in the culture medium (positive selection). The majority of the remaining cells, in which the entire construct (including the TK gene) inserts randomly, will die as a result of the incorporation of ganciclovir or fialuridine (inactive thymidine analogs), either of which blocks DNA synthesis. Homologous recombinant clones that do not contain the TK gene are used to prepare chimeric mice. Cells from these clones are microinjected into the fluid-filled cavity of 3.5-day-old embryos at the blastocyst stage. The injected embryos are then surgically transferred into the uterus of pseudopregnant females. These animals will give birth to chimeric mice. Breeding can be used to generate mice that are heterozygous and homozygous for the mutation. Homozygous mutants may express the gene of interest in any cell of the body (Figure 1-8).

Use of Mutant Mice in Studies of Brain Disease

Transgenic mice produced by this method are generally gain-of-function mutants, because the transgene is designed either to express a novel gene product or to disrupt a normal gene product by expressing a "dominant-negative" alternative. It is also possible to put a DNA fragment in the opposite direction and hence to produce transgenic mice expressing antisense RNA, which will reduce gene function (Jouvenceau *et al.* 1999; Katsuki *et al.* 1988). Expression of mutant amyloid precursor protein (APP) or presenilin 1 (PS1) or mutant forms of tau in mice has generated many animal models that may be related to Alzheimer's disease. These transgenic mice have facilitated studies of the pathogenesis, molecular mechanisms, and behavioral abnormalities of Alzheimer's disease (Bornemann and Staufenbiel 2000; Janus *et al.* 2001). Nevertheless, because the transgene integrates into the mouse genome randomly and often exists as several copies, the interpretation of studies with transgenic mice is difficult.

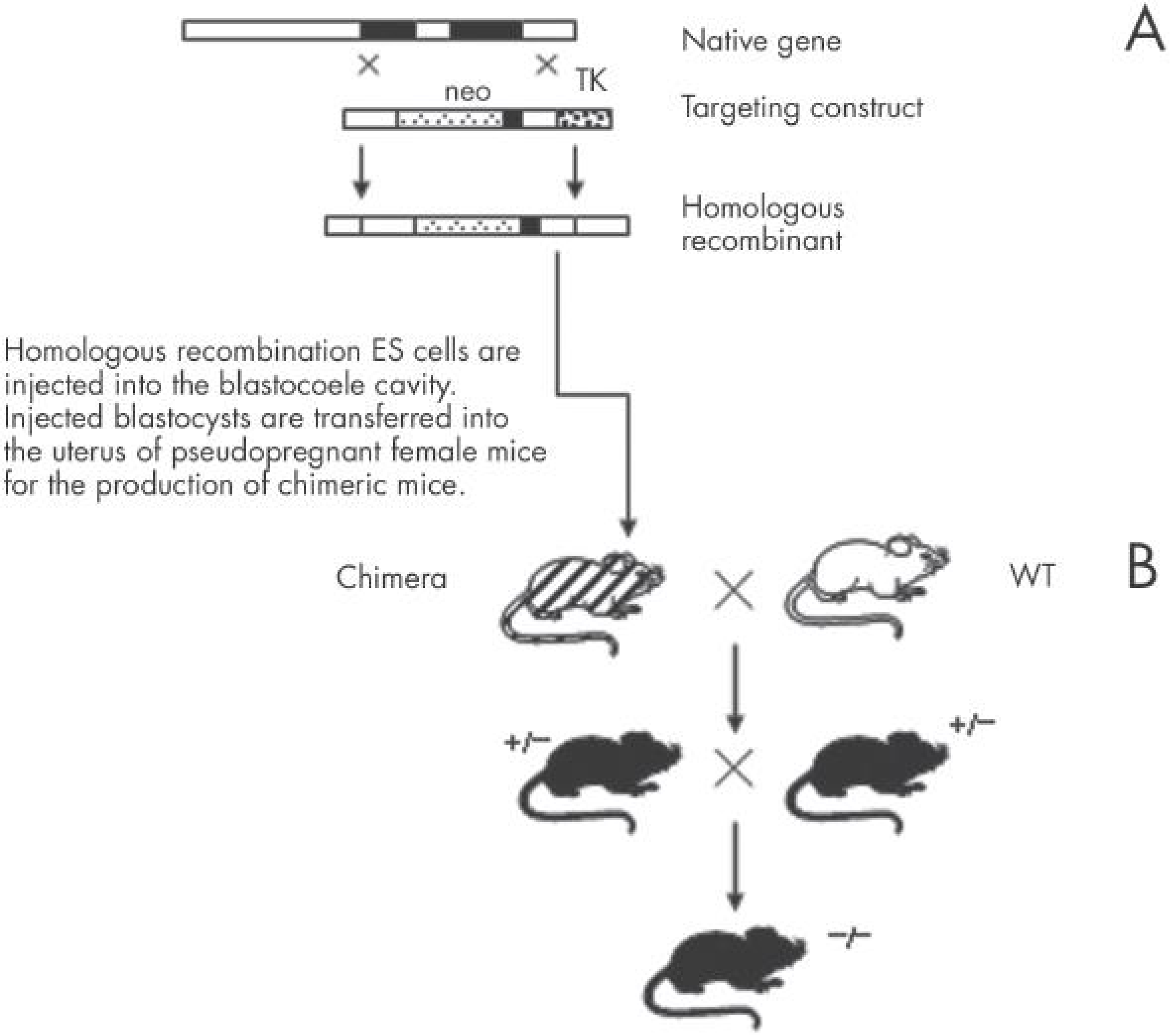

Native gene
A
neo
TK
Targeting construct
Homologous recombinant
Homologous recombination ES cells are injected into the blastocoele cavity. Injected blastocysts are transferred into the uterus of pseudopregnant female mice for the production of chimeric mice.
Chimera
WT
B
+/−
+/−
−/−

FIGURE 1-8. Conventional gene disruption ("knockout").

(A) Producing chimeric mice. First, a mutant allele is produced by replacing the coding exons of the desired gene with a neomycin (neo) cassette and transferred into embryonic stem (ES) cells. Second, genetically altered ES cells are reintroduced into a developing blastocyst, where they contribute to the developing embryo. **(B) Breeding chimeric mice.** When the germ cells of the resulting chimeric mouse (chimera) are ES cell-derived (germ-line mutation), the heterozygotes (+/[?]) can be produced by breeding. One-half of the offspring will be heterozygous. The heterozygous animals may be bred to produce homozygous mice ([?]/[?]). TK = thymidine kinase; WT = wild type.

Experiments with knockout mice have provided novel insights into the functional roles of neuronal genes and, in some cases, animal models relevant to brain disorders. The targeted mutants in a gene of interest, however, can sometimes lead to embryonic lethality in mice, thus obscuring the role of that gene in a specific tissue or in the adult. Furthermore, in some instances, genes related to the eliminated gene undergo increased expression in the knockout mice. In this case, the related gene compensates for the gene of interest and yields a phenotype that resembles the "normal" animal. Such compensation has been seen for the knockouts of the axonal microtubule-associated protein tau (Takei *et al.* 2000).

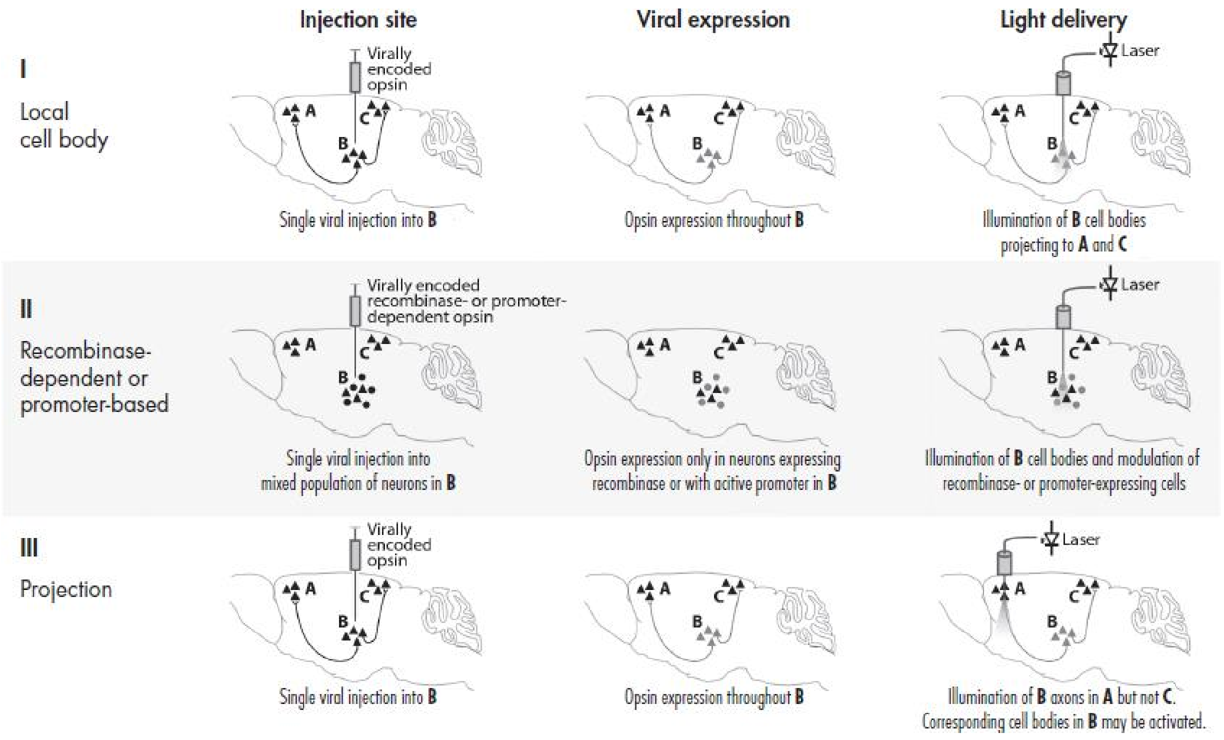
Tissue-Specific Gene Manipulation

A tissue-specific mechanism for gene targeting is the Cre-loxP system. Both the Cre (cyclization recombination) recombinase and loxP sequences are derived from the P1 bacteriophage, which uses this recombination system in its life cycle to maintain the phage genome as a unit copy plasmid in the lysogenic state. The Cre-loxP system enables the specific manipulation of DNA based on the direction and location of the two loxPs. As a member of the integrase superfamily of site-specific recombinases, the Cre recombinase does not require any host cofactors or accessory proteins to mediate loxP-specific recombination. In most cases, loxP sites are placed in the same chromosome in direct repeat positions so that the intervening DNA sequence can be deleted. The loxP sites can also be placed in different chromosomes to promote recombination between different chromosomes, or they can be placed in an inverted position in the same chromosome to create a switch to inactivate and activate genes of interest (Bouabe and Okkenhaug 2013).

For conditional site-specific genome modification, two mouse lines are usually needed: 1) mice that have the DNA sequence of interest flanked by loxP sites (or "floxed"), which can be achieved by introducing loxP sites into the genomic locus of interest by homologous recombination as described in the previous paragraph, and 2) Cre recombinase transgenic mice, in which Cre is expressed under the control of a promoter that is active in specific cell types or tissues, or in which Cre is transiently expressed under the control of a promoter that is active at a particular developmental stage of tissues or cells. Cre expression can also be controlled temporally, by introducing an element into the promoter, which requires a ligand, such as a drug, for induction. When mice carrying such "floxed" genes are mated with transgenic mice expressing Cre recombinase, the target gene of the offspring is modified through Cre action in the cell types or tissues where Cre is expressed, or in the cell or tissue when the mouse is treated with a drug, such as tamoxifen (Bouabe and Okkenhaug 2013; Friedel *et al.* 2011; Liu *et al.* 2014). Studies in which the *N*-methyl-D-aspartate (NMDA) receptor gene *NR1* was deleted from specific hippocampal loci using Cre-loxP recombination technology reveal that a regional variation in NMDA receptor-dependent synaptic plasticity of postnatal excitatory neurons is required for specific aspects of hippocampal learning and memory (McHugh *et al.* 2007; Nakazawa *et al.* 2003).

Optogenetics and Chemogenetics

Optogenetics is a technique for parsing and manipulating specific neural circuits (Figure 1-9). Since its inception, optogenetics has been adapted both swiftly and broadly (Deisseroth 2015) and applied to psychiatric research (Shirai and Hayashi-Takagi 2017). Optogenetics makes use of microbial (bacterial and algal) opsins that have properties of both chromophores and ion channels. These molecules are unlike the metazoan rhodopsins, which convert light into an intracellular signal through a G protein-coupled receptor. Instead, these proteins (channelopsins and bacteriorhodopsin) form ion channels, and there are naturally occurring molecules that subserve both excitatory (Na^{+}) and inhibitory ($\text{Cl}^{[?]}$) functions, as activated by the channels.


Injection site
Viral expression
Light delivery
I
Local cell body
Virally encoded opsin
Laser
A
B
C
Single viral injection into B
Opsin expression throughout B
Illumination of B cell bodies projecting to A and C
II
Recombinase-dependent or promoter-based
Virally encoded recombinase- or promoter-dependent opsin
Single viral injection into mixed population of neurons in B
Opsin expression only in neurons expressing recombinase or with acitive promoter in B
Illumination of B cell bodies and modulation of recombinase- or promoter-expressing cells
III
Projection
Virally encoded opsin
Single viral injection into B
Opsin expression throughout B
Illumination of B axons in A but not C. Corresponding cell bodies in B may be activated.

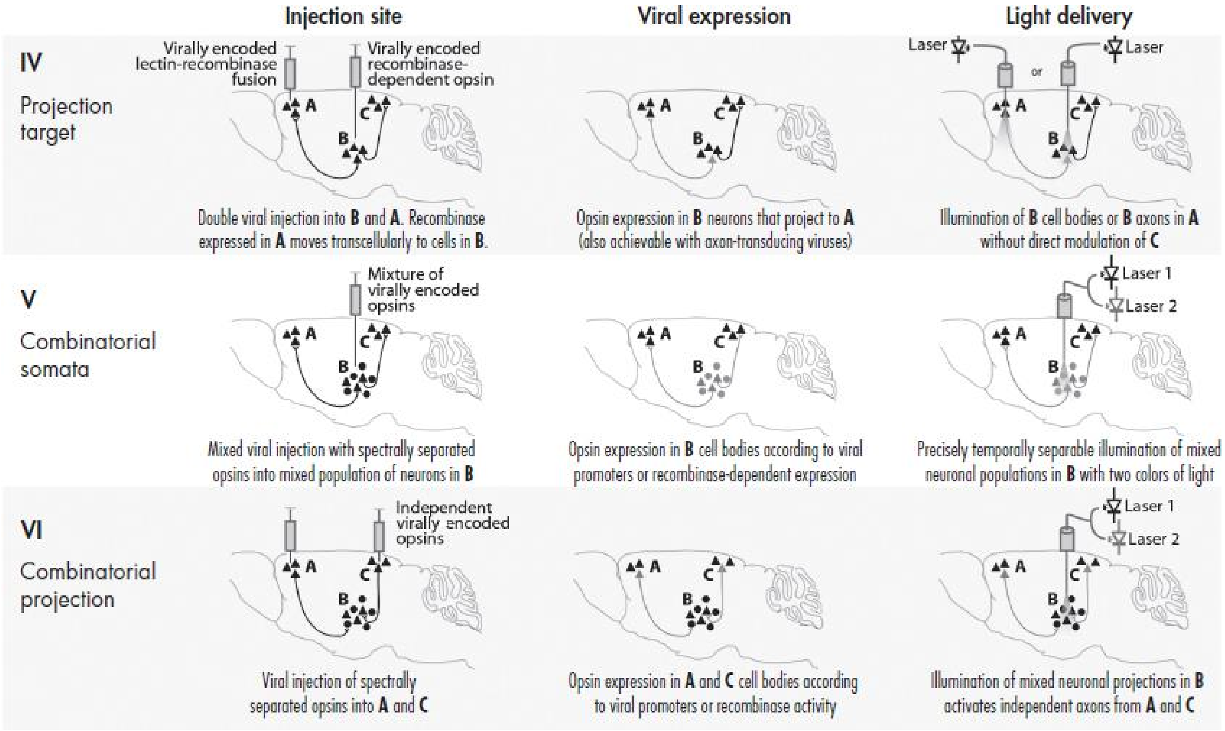

Injection site
Viral expression
Light delivery
IV
Projection target
Virally encoded lectin-recombinase fusion
Virally encoded recombinase-dependent opsin
Laser
or
Laser
A
B
C
Double viral injection into B and A. Recombinase expressed in A moves transcellularly to cells in B.
Opsin expression in B neurons that project to A (also achievable with axon-transducing viruses)
Illumination of B cell bodies or B axons in A without direct modulation of C
V
Combinatorial somata
Mixture of virally encoded opsins
Laser 1
Laser 2
Mixed viral injection with spectrally separated opsins into mixed population of neurons in B
Opsin expression in B cell bodies according to viral promoters or recombinase-dependent expression
Precisely temporally separable illumination of mixed neuronal populations in B with two colors of light
VI
Combinatorial projection
Independent virally encoded opsins
Laser 1
Laser 2
Viral injection of spectrally separated opsins into A and C
Opsin expression in A and C cell bodies according to viral promoters or recombinase activity
Illumination of mixed neuronal projections in B activates independent axons from A and C

FIGURE 1-9. Optogenetic manipulation of neural circuits.

See Plates 2 and 3 to view this figure in color.

(I) Direct stimulation of neuronal cell bodies is achieved by injecting virus at the target region and then implanting a light-delivery device above the injected region. Even this simple experiment can provide specificity with viruses that will not transduce afferent axons and fibers of passage. **(II)** Additional cell-type specificity is attained either by cell-type-specific promoters in the viral vector or via a recombinase-dependent virus, injected in a transgenic animal expressing a recombinase such as Cre in specific cells, leading to specific expression of the transgene only in defined cell types. **(III)** Projection (axonal) targeting is achieved by viral injection at the region harboring cell bodies, followed by implantation of a light-delivery device above the target region containing neuronal processes from the virally transduced region; in this way, cell types are targeted by virtue of their projections. **(IV)** Projection termination labeling is a more refined version of projection targeting, in which cells are targeted by virtue of synaptic connectivity to the target region, with likely exclusion of cells whose axons simply pass through the region. Transcellular labeling using a recombinase-dependent system is shown. Viruses expressing Cre fused to a trans-neuronal tracer (lectin) are delivered at the synaptic target site, and a Cre-dependent virus is injected into the region with cell bodies. Cells that project to the Cre-injected area express the Cre-dependent virus and become light sensitive. Transcellular labeling can also be achieved with axon terminal-transducing viruses, although without control over the postsynaptic cell type. **(V)** Expression of two opsins with different characteristics in one brain region using a combination of promoter-or Cre-based approaches. Light delivery to the somata is performed using two different wavelengths designed to minimize cross-activation. **(VI)** Projections from two different brain regions are differentially stimulated with two wavelengths matched to the respective opsins expressed upstream.

Source. Adapted from Figure 2 (p. 18) in Yizhar O, Fenno LE, Davidson TJ, et al.: "Optogenetics in Neural Systems." *Neuron* 71(1):9-34, 2011 (https://doi.org/10.1016/j.neuron.2011.06.004). Copyright (c) 2011, Elsevier, Inc. Used with permission.

The ingenious application that initially launched optogenetics toward worldwide adaptation was an engineered system that allowed both specificity of expression and specificity of excitation. This tool allowed an investigator to inject a virus encoding a channelrhodopsin activated by a specific wavelength of light and a targeting vector restricting expression to a certain class of cells (e.g., serotonergic) within a defined brain region. Introduction of a fiberoptic cable into the area of injection permitted the activation of the channelrhodopsin (and the subsequent activation or inhibition of the neuron containing that rhodopsin) by light. As the technique was further refined, channel opsins responsive to different wavelengths were expressed so that, depending on the wavelength used, different cells within a similar anatomic locus could be selectively activated or inhibited. The readout from such experiments could be anything from electrophysiological to behavioral.

A similar technology uses chemogenetics to control the activity of neuronal subpopulations in transgenic animal models. In chemogenetics, Cre-inducible viral vectors can be used to express *designer receptors exclusively activated by designer drugs* (DREADDs). Inhibitory or excitatory DREADDs (Armbruster *et al.* 2007; Krashes *et al.* 2011) are pharmacologically activated by the biologically inert ligand clozapine-*N*-oxide (CNO), where upon binding, CNO triggers an inhibitory (G_i) or excitatory (G_q) or intracellular signaling (G_s) cascade driven by a mutant G protein-coupled receptor (GPCR). As optogenetic and chemogenetic approaches continue to be refined, the ability to translate from cells to circuits to behavior will increase in both complexity and resolution.

Proteomics and Beyond

The large-scale analysis of proteins in biological systems is critical to understanding the functional output of transcriptomic programs. Since mRNA levels can only approximate protein levels and the activity of proteins is often regulated through posttranslational modifications including phosphorylation and ubiquitination, proteomic analyses provide important insights that would otherwise be missed using genomic, epigenetic, and transcriptomic approaches. Increasingly, bioinformatic tools, including machine learning, are used to integrate and analyze large datasets produced through "multi-omics" to gain a more thorough understanding of complex biological systems and disease states.

Proteomics is a broad discipline where protein structure, function, interactions, posttranslational modifications, or expression levels are interrogated. Generally, protein expression profiling involves the ionization and analysis of proteins by mass spectrometry.

Conclusion

Increased knowledge of the human genome and advances in the methodology for genetic manipulation are continuously combining with advances in neurobiology. We are accumulating knowledge of human gene mutations and their possible connections to neurological and psychiatric diseases at a rapid pace. Rationally designed genome-based therapeutics are, in particular, emerging for monogenic (single gene locus-associated) disorders or cancers with single drivers. Increasing attention is today given by researchers to many gene regulatory mechanisms and to regions of the genome outside the classic protein-coding genes. However, the complexity of the genome, and its regulation, continues to pose challenges to our understanding of the true pathogenic mechanisms for complex polygenic diseases.

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CHAPTER 2

Neurotransmitters, Receptors, and Transporters

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Most if not all drugs, as well as other types of treatments, for psychiatric disorders work initially by modifying the process of synaptic transmission. As first described by Cajal and Sherrington, nerves are able to communicate with each other even though there is a very small space, termed the synapse, separating them. This space is about 30 nanometers wide--about 1/1,000 the width of a human hair. In view of such a small space, it is not surprising that there was an intense debate about the mechanism of synaptic transmission. One school of thought held that the mechanism was "electrical," whereby the action potential invading the presynaptic nerve terminal could directly activate the neuron on the other side of the synapse, the postsynaptic one. The other school of thought held that it was "chemical," such that chemicals were released from the activated presynaptic neuron, diffused across the synapse, and either activated or inhibited activity in the postsynaptic neuron by acting on receptors located on it. This debate has been referred to, somewhat facetiously, as "war of the soups versus sparks" (Valenstein 2005). There is now essentially universal agreement that the process of synaptic transmission is chemical in nature, at least in the mammalian central nervous system (CNS). Not surprisingly, the chemicals involved are called *neurotransmitters*. In this chapter we focus on the neurotransmitters considered to be involved in psychiatric disorders and their treatment as well as the receptors by which they produce their effects. Figure 2-1 shows the structures of neurotransmitters discussed in this chapter.

Neurotransmitters

Criteria have been established that must be fulfilled for a chemical to be considered a neurotransmitter:

1. The chemical is present (synthesized and stored) in neurons.
2. The chemical is released from neurons.
3. When administered exogenously, the chemical mimics precisely the action of the endogenously released chemical.
4. Specific mechanisms exist for removing the chemical from the synapse to terminate its activity there.

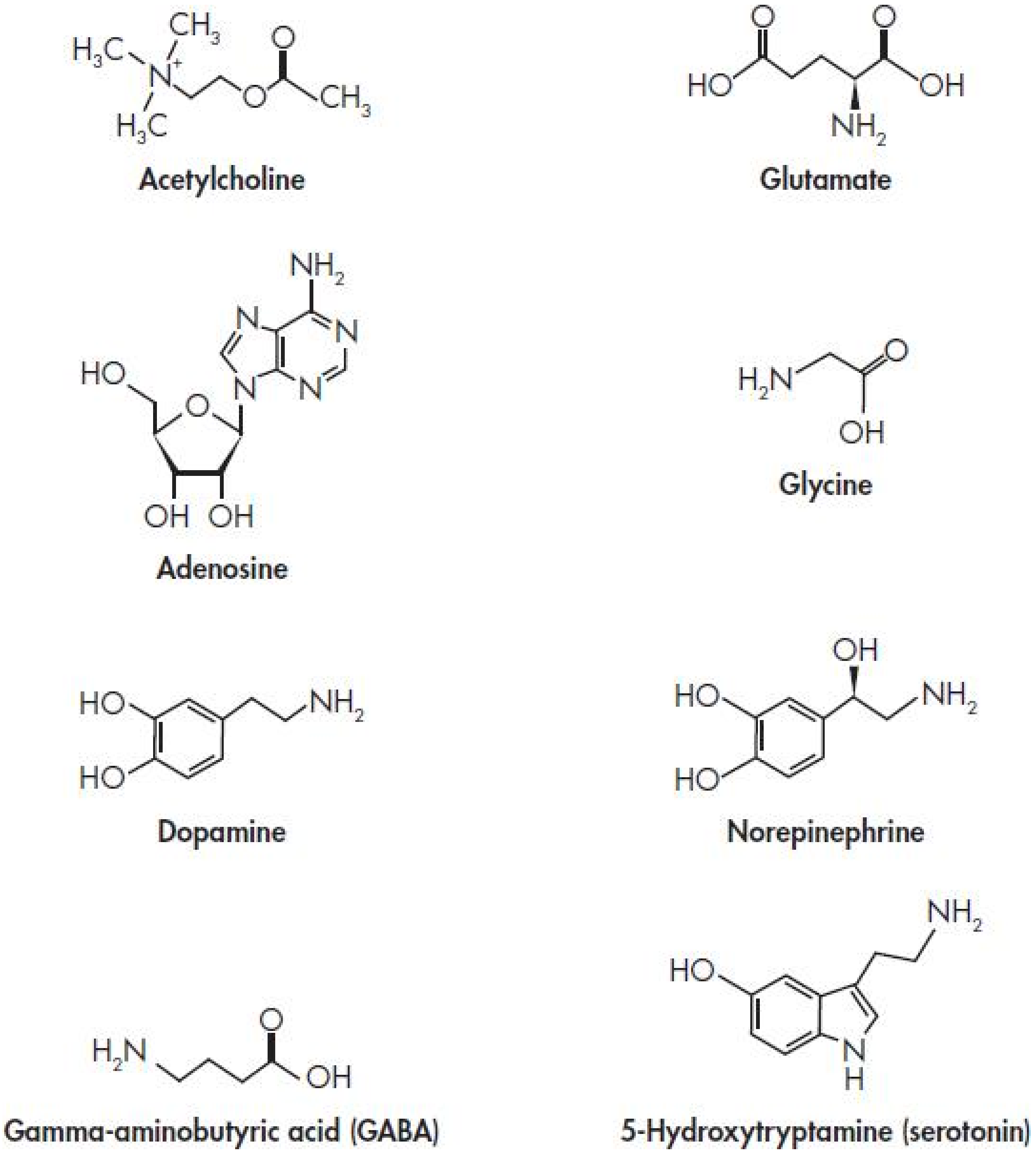
Many chemicals have been identified as neurotransmitters, and the numbers have increased as the definition of a neurotransmitter has been extended to include neuromodulators and neurohormones. And not only are there multiple neurotransmitters, but for each neurotransmitter, there are many different receptors. With 100 billion neurons and 10-to 50-fold more glial cells, it is no wonder that the human brain is considered to be the most complex organ in the body and even the most complex structure in the world.

The different transmitters and their receptors allow for specificity in modifying synaptic transmission. This contrasts with the process of neuronal conduction, which is similar for all neurons. Alteration of neuronal conduction (e.g., via administration of general or local anesthetics) produces nonspecific effects. By contrast, more specific effects can be produced by modifying the actions of different neurotransmitters, which is desirable when considering the treatment of psychiatric disorders.

Receptors

Intercellular communication is a requirement for multicellular organisms to maintain homeostasis and to respond appropriately to the environment. Receptors are proteins that allow cells to respond to chemical signals from other cells and from the environment, such as those carried by neurotransmitters, hormones, and sensory stimuli. In general, such signals lead to a conformational change in the receptor protein that allows the receptor to alter cellular function. In the CNS, receptors can be found on the plasma membrane or in intracellular compartments in both neurons and glial cells (e.g., oligodendrocytes, astrocytes, microglia). Most neurotransmitter receptors are cell surface receptors and consist of three major classes: ionotropic receptors, seven-transmembrane-spanning (also known as G protein-coupled) receptors, and tyrosine kinase receptors. As will be discussed in more detail below, the conformational change in ionotropic receptors in response to neurotransmitter binding results in a change in ion permeability, thereby altering (increasing or decreasing) cell excitability. Neurotransmitter activation of receptor tyrosine kinases increases the kinase activity of the protein, resulting in phosphorylation of the receptor itself (autophosphorylation) along with phosphorylation

of secondary signaling molecules that lead to changes in cell function. Conformational changes in seven-transmembrane-spanning receptors by neurotransmitter binding allow the receptors to interact with secondary molecules (transducers), such as guanine nucleotide-binding proteins (G proteins), arrestins, and others, to regulate cellular function. An excellent resource for detailed information on the many subtypes of cell surface receptors and neurotransmitters (along with many other important pharmacological components) that is updated regularly can be found at the website of the International Union of Basic and Clinical Pharmacology/British Pharmacological Society (IUPHAR/BPS) Guide to Pharmacology (www.guidetopharmacology.org).



Acetylcholine

Glutamate

Adenosine

Glycine

Dopamine

Norepinephrine

Gamma-aminobutyric acid (GABA)

5-Hydroxytryptamine (serotonin)

FIGURE 2-1. Structures of neurotransmitters.

Ionotropic Receptors

The first class of receptors described in this chapter are ion channel (or ionotropic) receptors. These receptors are quite literally pores in the cellular membrane that are permeable to specific ions. When these receptors/pores are open, ion channels permit the passive diffusion of ions down their concentration (and electrical) gradient. The beginning of our understanding of ion channel function came from Alan Hodgkin and Andrew Huxley, who worked together in the 1940s and 1950s and received a Nobel prize for their research (Hodgkin and Huxley 1952). Using the giant axon of a squid, they measured the membrane potential of a neuron and recorded the first intracellular action potential (Hodgkin and Huxley 1952). These and subsequent studies revealed that the concentrations of ions inside and outside of a neuron are not in equilibrium. Rather, in the CNS, the concentrations of Na^+, Ca^{2+}, and $Cl^{[?]}$ are much higher outside the cell, whereas the opposite is true for the concentrations of K^+. This concentration gradient is generated, in part, by the plasma membrane sodium-potassium adenosine triphosphatase (Na^+/K^+ ATPase) and provides the foundation for ionotropic receptor signaling (Figure 2-2). Ligand-gated ion channels undergo a conformational change when a molecule (ligand) binds, resulting in the opening of a pore in the membrane. If the ionotropic receptors are permeable to Na^+ or Ca^{2+}, positively charged ions will flow down the concentration gradient into the neuron, resulting in depolarization. Conversely, opening of ionotropic receptors permeable to K^+ or to $Cl^{[?]}$ leads to hyperpolarization due to an efflux of positive or an influx of negative ions, respectively (see Figure 2-2). Ligand-gated ion channels are described later in the chapter and include receptors for glutamate (e.g., the NMDA [*N*-methyl-D-aspartate] receptor; see "Glutamatergic System"), g-aminobutyric acid (e.g., the $GABA_A$ receptor; see "GABAergic System"), acetylcholine (e.g., the nicotinic acetylcholine receptor; see "Cholinergic System"), and serotonin (e.g., the 5-hydroxytryptamine [5-HT] type 3 [$5\text{-}HT_3$] receptor; see "Serotonergic System").

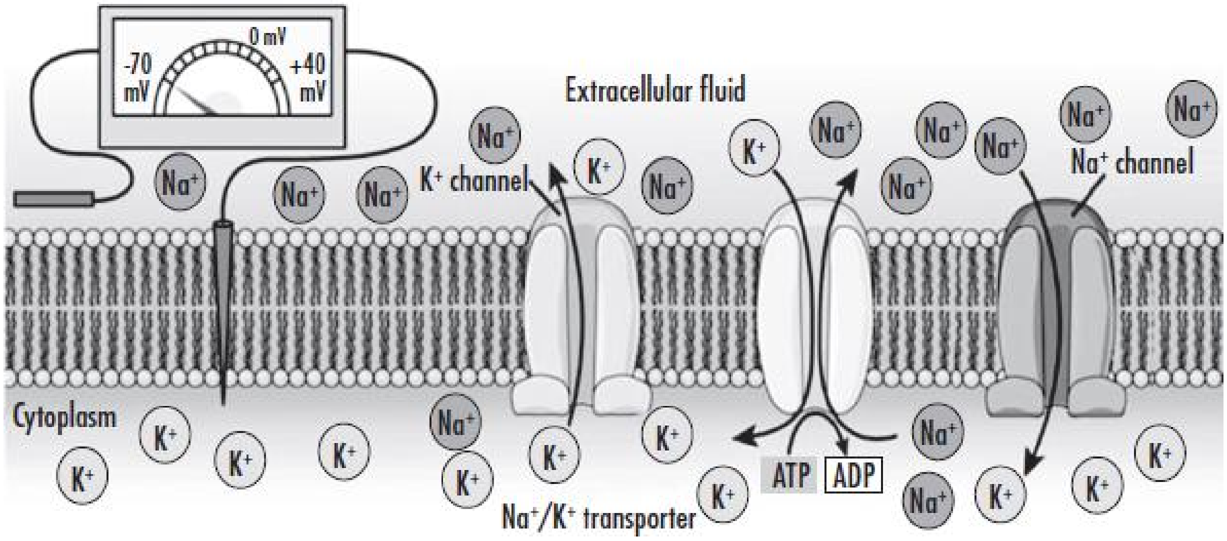


FIGURE 2-2. Ion channel function in the CNS.

See Plate 4 to view this figure in color.

The plasma membrane Na^+/K^+ ATPase establishes a concentration gradient in the CNS, pumping Na^+ out and K^+ into the cell. Ion channels permit the passive diffusion of ions across the plasma membrane. Thus, opening of Na^+ channels depolarizes--and of K^+ channels hyperpolarizes--a neuron. ADP = adenosine diphosphate; ATP = adenosine triphosphate; mV = millivolt.

Source. Reprinted from Figure 35.10c (Hyperpolarization) in Biology 2e. Provided under a Creative Commons Attribution 4.0 license (CC BY 4.0) by OpenStax (https://openstax.org/books/biology-2e/pages/1-introduction).

The ability to move ions across the membrane stems from the physical properties of the channel. In the case of ionotropic receptors, various subunits of the receptor combine in the membrane to form a pore. There are often multiple receptor subunits for a single class of ionotropic receptor. For example, the $GABA_A$ receptor is assembled as a pentameric structure from at least 19 different subunits, resulting in distinct functional and anatomical distributions (Olsen and Sieghart 2009). This heterogeneity provides a system with considerable flexibility. For example, there is research into the potential development of $GABA_A$ receptor modulators that produce an anxiolytic effect devoid of sedation, or as a novel class of antidepressant medication by targeting distinct subunits present in selected brain regions. The benefit of targeting ionotropic receptors is that their effects are rapid (ion channels open and close within milliseconds) and regulate both fast excitatory and inhibitory synaptic signaling in the CNS. As discussed in the "Neurotransmitter and Neuropeptide Systems" section later in this chapter, many of the classical neurotransmitters (e.g., monoamines) exert their effects on a slower time scale and are therefore often considered to be modulatory.

G Protein-Coupled Receptors

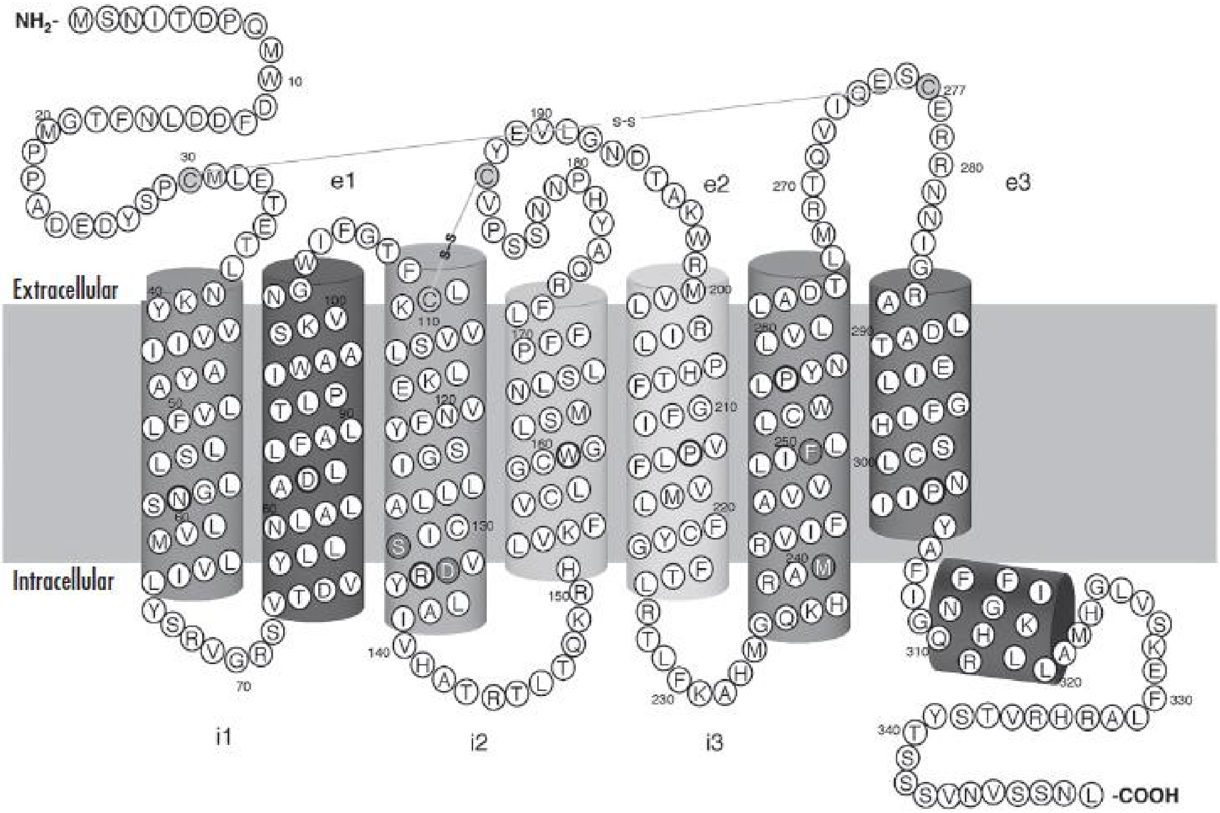
As the name *G protein-coupled receptor* (GPCR) implies, these receptor proteins couple to heterotrimeric guanine nucleotide-binding proteins (G proteins). However, it is now well established that GPCRs can interact with and signal via a variety of signaling partners, such as G proteins, arrestins, and others. For this reason, it may be more appropriate to call these receptors *seven-transmembrane-spanning receptors*; nevertheless, the term *GPCR* is entrenched in the literature.

GPCRs are the largest family of cell surface receptors and are a major target for pharmaceuticals (Wacker *et al.* 2017), especially in psychiatry (Catapano and Manji 2007; Grammatopoulos 2017). In humans, there are approximately 800 GPCRs, which can be subdivided into five families (Rhodopsin, Secretin, Glutamate, Adhesion, and Frizzled) based on amino acid sequence homology. More than half of these receptors are involved in processing sensory information (light, olfaction, taste, and pheromones), and the vast majority of these (~ 400) are olfactory receptors. The remaining receptors (~ 350) are activated by a wide variety of molecules--ranging in size from ions (e.g., calcium) to proteins (e.g., luteinizing hormone)--and include neurotransmitters important for CNS function, such as glutamate, GABA, norepinephrine, dopamine, serotonin, and acetylcholine.

The role of a GPCR is to detect the presence of an extracellular signaling molecule and subsequently change cellular function. GPCRs are involved in regulating a broad array of physiological functions and behaviors, which makes them ideal as targets for drugs. In fact, about 35% of U.S. Food and Drug Administration (FDA)-approved drugs target GPCRs (Insel *et al.* 2019). However, because the FDA-approved drugs act on fewer than 50% of the nonsensory GPCRs (Yang *et al.* 2021), there is considerable opportunity for development of new drugs to target other GPCRs.

All GPCRs have similar structural characteristics and consist of a single polypeptide chain of amino acids, with an extracellular N-terminus and an intracellular C-terminus, that traverse the membrane seven times (Figure 2-3). The well-conserved transmembrane hydrophobic domains are alpha helices, consisting of 25-35 amino acids each. These transmembrane domains are connected by three extracellular and three intracellular loops of amino acids that vary considerably in length. Due to posttranslational modifications, some GPCRs (~ 70%) have a fourth intracellular loop as a result of reversible palmitoylation of cysteine residues in the C-terminal domain (Naumenko and Ponimaskin 2018). Palmitoylation--and other posttranslational

modifications (e.g., phosphorylation, acylation, glycosylation, ubiquitination, sumoylation) of amino acids in various parts of a GPCR--can markedly alter signaling and trafficking of the targeted receptor (Patwardhan *et al.* 2021).


NH2-
-COOH
Extracellular
Intracellular
e1
e2
e3
i1
i2
i3
S-S
10
20
30
40
50
60
70
90
100
110
120
130
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310
320
330
340

FIGURE 2-3. Amino acid sequence of the CXC chemokine receptor 1 (CXCR1) G protein-coupled receptor (GPCR).

The CXCR1 consists of characteristic seven-transmembrane helices (TM1-TM7) connected by three extracellular loops (e1-e3) and three intracellular loops (i1-i3). The disulfide bond between the cysteine residues of e1 and e2 is also characteristic of GPCRs.

Source. Modified from Figure 1 (p. 183) in Han X, Feng Y, Chen X, et al.: "Characterization of G Protein Coupling Mediated by the Conserved D134(3.49) of DRY Motif, M241(6.34), and F251(6.44) Residues on Human CXCR1." *Federation of European Biochemical Societies (FEBS) Open Bio* 5:182-190, 2015 (https://doi.org/10.1016/j.fob.2015.03.001). Copyright (c) 2015, The Authors. Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies. This is an open access article under the Attribution-NonCommercial-No Derivatives 3.0 United States (CC BY-NC-ND 3.0 US) license (https://creativecommons.org/licenses/by-nc-nd/3.0/us/).

GPCRs are activated by a wide variety of extracellular chemical signals that bind to and stabilize an active conformation of the receptor capable of interacting with intracellular signaling molecules (transducers), including G proteins and arrestins. Ligands bind to an extracellular-facing binding pocket (known as the orthosteric binding site), the location of which differs widely for different receptors. For some receptors (e.g., biogenic amine receptors such as serotonin, norepinephrine, and dopamine), the orthosteric binding pocket is located within the transmembrane domains. For others, the ligand binds to a pocket in the N-terminal domain (e.g., glutamate family), to amino acids in the extracellular loops, or to both the N-terminal domain and extracellular loops.

If a ligand has positive intrinsic efficacy (i.e., an agonist), ligand binding results in receptor activation. Receptor activation involves reorientation of transmembrane helices (outward movement of transmembrane domain 6), which promotes interaction of the receptor with its transducing partners (see "GPCR transducing proteins") (Zhou *et al.* 2019), thereby leading to changes in cell function. It also should be pointed out that GPCRs can adopt an active conformation spontaneously in the absence of the binding of an activating ligand. This type of ligand-independent activation is called *constitutive receptor activity* and will be discussed in more detail below (see "Constitutive Receptor Activity").

In addition to orthosteric binding, ligands can bind to other sites on a receptor that are referred to as *allosteric* binding sites ("allo" means "other"). Such ligands are called *allosteric modulators* or *allosteric regulators*. Allosteric modulators act by changing the conformation of the receptor in a way that causes the ligand binding affinity and/or intrinsic efficacy to be altered (Gentry *et al.* 2015; Kenakin 2021; Wenthur *et al.* 2014). In a way, a receptor with an allosteric modulator bound is a different receptor. The conformational change in the receptor produced by allosteric ligand occupancy can differentially alter the affinity and/or the intrinsic efficacy of an orthosteric ligand in a ligand-dependent manner (i.e., the allosteric effect can be different for different ligands). This is known as *probe dependence* (wherein the orthosteric ligand is considered the "probe"). Allosteric ligands that increase orthosteric ligand affinity and/or intrinsic efficacy are called *positive allosteric modulators* (PAMs). Conversely, those that decrease orthosteric affinity and/or intrinsic efficacy are referred to as *negative allosteric modulators* (NAMs). It is important to note that because of probe dependence, the designation as PAM or NAM is dependent on the specific orthosteric ligand. Thus, the same allosteric modulator can be a NAM for one orthosteric ligand but a PAM for another. Because allosteric regulators do not block the orthosteric binding site, they "fine-tune" receptor function, allowing for the natural pattern/rhythm of endogenous agonist activity. Also, adverse effects associated with complete abolition of orthosteric binding to the receptor are avoided; thus, allosteric ligands are considered to be safer than orthosteric drugs. Because allosteric binding sites on a receptor are less conserved than orthosteric sites, allosteric ligands are also more selective than orthosteric ligands and can often distinguish between highly homologous receptors. There is great optimism for the discovery of new therapeutic medications that are allosteric modulators.

Unlike other cell surface receptors where the receptor is itself an effector (e.g., ligand-gated ion channels, receptor tyrosine kinases), activated GPCRs by themselves do not change cellular function. GPCRs must interact with a partner molecule (a transducer) in order to signal. Perhaps the best-studied transducers are the heterotrimeric G proteins.

GPCR Transducer Proteins: G Proteins and Arrestins

G proteins. The G proteins that couple to GPCRs consist of three subunits (heterotrimeric): alpha (a), beta (b), and gamma (g). In general, the b and g subunits are tightly bound to each other and form a functional unit that is commonly referred to as the b/g subunit. In humans, there are 21 a, 6 b, and 12 g subunits that combine to form a wide variety of heterotrimers. The a subunits bind guanine nucleotides, such as guanosine diphosphate (GDP) and guanosine triphosphate (GTP)--hence the name *guanine nucleotide-binding protein*. In addition to binding guanine nucleotides, the a subunit is also an enzyme that hydrolyzes GTP (GTPase) to remove the terminal phosphate, resulting in the formation of GDP. As transducer proteins, G proteins relay the signal from an activated GPCR to cellular effector proteins that are responsible for effecting a change in cell function. G proteins regulate a wide variety of effectors, including adenylyl cyclases, phospholipase C, various kinases, scaffold proteins, and ion channels (Figure 2-4).

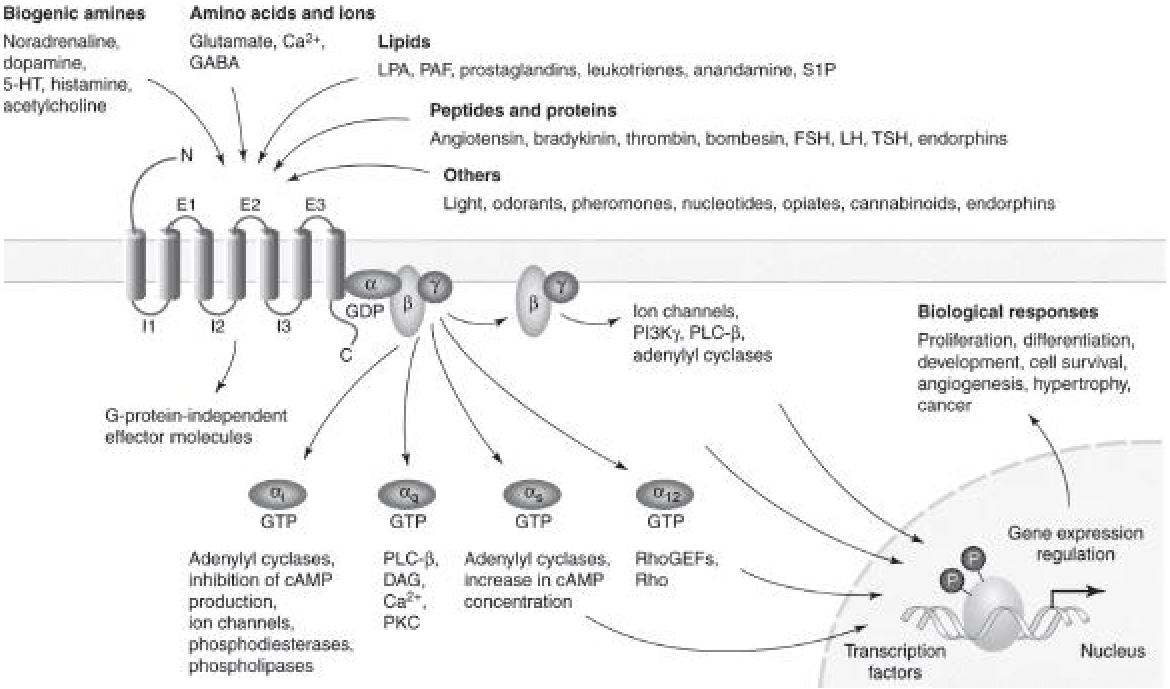

Biogenic amines
Noradrenaline, dopamine, 5-HT, histamine, acetylcholine
Amino acids and ions
Glutamate, Ca2+, GABA
Lipids
LPA, PAF, prostaglandins, leukotrienes, anandamine, S1P
Peptides and proteins
Angiotensin, bradykinin, thrombin, bombesin, FSH, LH, TSH, endorphins
Others
Light, odorants, pheromones, nucleotides, opiates, cannabinoids, endorphins
N
E1
E2
E3
I1
I2
I3
C
α
GDP
β
γ
G-protein-independent effector molecules
Ion channels, PI3Kγ, PLC-β, adenylyl cyclases
Biological responses
Proliferation, differentiation, development, cell survival, angiogenesis, hypertrophy, cancer
αi
GTP
αq
GTP
αs
GTP
α12
GTP
Adenylyl cyclases, inhibition of cAMP production, ion channels, phosphodiesterases, phospholipases
PLC-β, DAG, Ca2+, PKC
Adenylyl cyclases, increase in cAMP concentration
RhoGEFs, Rho
Gene expression regulation
P
P
Transcription factors
Nucleus

FIGURE 2-4. Diversity of G protein-coupled receptors (GPCRs).

See Plate 5 to view this figure in color.

A wide variety of ligands, including biogenic amines, amino acids, ions, lipids, peptides, and proteins, use GPCRs to stimulate cytoplasmic and nuclear targets through heterotrimeric G-protein-dependent and -independent pathways. Such signaling pathways regulate key biological functions such as cell proliferation, cell survival, and angiogenesis. 5-HT = 5-hydroxytryptamine; C = carboxy terminus; cAMP = cyclic adenosine monophosphate; E1, E2, E3 = extracellular loop 1, 2, 3; DAG = diacylglycerol; FSH = follicle-stimulating hormone; GDP = guanosine diphosphate; GEF = guanine nucleotide exchange factor; GTP = guanosine triphosphate; I1, I2, I3 = intracellular loop 1, 2, 3; LH = luteinizing hormone; LPA = lysophosphatidic acid; N = amino terminus; P = phosphorus; PAF = platelet-activating factor; PI3K = phosphatidylinositol 3-kinase g; PKC = protein kinase C; PLC-b = phospholipase C-b; S1P = sphingosine-1-phosphate; TSH = thyroid-stimulating hormone.

Source. Reprinted from Figure 1 (p. 368) in Marinissen MJ, Gutkind JS: "G-Protein-Coupled Receptors and Signaling Networks: Emerging Paradigms." *Trends in Pharmacological Sciences* 22(7):368-376, 2001 (https://doi.org/10.1016/S0165-6147(00)01678-3). Copyright (c) 2001, Elsevier Science Ltd. Used with permission.

G proteins are divided into four families based on the identity of the a subunit, and each subfamily has multiple members (Table 2-1). Although initially thought to be an inert holding protein for a subunits, the b/g subunit is now recognized to also play a major role in regulating cellular effectors, including ion channels, adenylyl cyclases, phospholipases A and C, G protein receptor kinase 2, and phosphoinositide 3-kinase, among others (Smrcka and Fisher 2019).

TABLE 2-1. Heterotrimeric G protein subunits: function and expression

Family	Subtypes	Major effectors	Expression
G_sa	$G_{s(S)}$a	Adenylyl cyclase (activation)	G_sa: ubiquitous
	$G_{s(L)}$a	Maxi-K^+ channel (activation)	G_{olf}a: olfactory neurons, certain CNS ganglia; digestive and urogenital tract
	$G_{s(XL)}$a	Src tyrosine kinase (activation)	
	G_{olf}a		
$G_{i/o}$a	$G_{o1,o2}$a	Adenylyl cyclase (inhibition)	$G_{o1\text{-}o2}$a: neurons, neuroendocrine cells, astroglia, heart

Note. ERK = extracellular signal-regulated kinase; GIRK = G protein-coupled inwardly rectifying potassium [channel]; iNOS = inducible nitric oxide synthase; MAPK = mitogen-activated protein kinase; Maxi-K^+ = large-conductance calcium-activated potassium channel; NHE-1 = sodium-hydrogen antiporter 1.

Source. Adapted from Table 1 (p. S48) in Milligan G, Kostenis E: "Heterotrimeric G-proteins: A Short History." *British Journal of Pharmacology* 147(Suppl 1):S46-S55, 2006. Copyright (c) 2006, Nature Publishing Group (www.nature.com/bjp); Open Access. *British Journal of Pharmacology* Open Access articles are published under the terms of the Creative Commons Attribution License. The CC BY license permits commercial and non-commercial re-use of an open access article as long as the author is properly attributed.

Family	**Subtypes**	**Major effectors**	**Expression**
	$G_{i1\text{-}i3}a$	Ca^{2+} (N-, P/Q-, R-type) channels (inhibition)	$G_{i1\text{-}i3}a$: neurons and many other cell types
	$G_{z}a$	K^{+} (GIRK) channel (activation)	$G_{z}a$: platelets, neurons, adrenal chromaffin cells, neurosecretory cells
	$G_{t1,t2}a$	ERK/MAPK (activation)	$G_{t1}a$: rod outer segments, taste buds
	$G_{gust}a$		$G_{t2}a$: cone outer segments
			$G_{gust}a$: sweet and/or bitter taste buds, chemoreceptor cells in the airway
$G_{q/11}a$	$G_{q}a$	Phospholipase Cb (activation)	$G_{q/11}a$: ubiquitous
	$G_{11}a$	Bruton's tyrosine kinase (activation)	$G_{15/16}a$: hematopoietic cells
	$G_{14}a$		
	$G_{15}a$		
	$G_{16}a$		

Note. ERK = extracellular signal-regulated kinase; GIRK = G protein-coupled inwardly rectifying potassium [channel]; iNOS = inducible nitric oxide synthase; MAPK = mitogen-activated protein kinase; Maxi-K^{+} = large-conductance calcium-activated potassium channel; NHE-1 = sodium-hydrogen antiporter 1.

Source. Adapted from Table 1 (p. S48) in Milligan G, Kostenis E: "Heterotrimeric G-proteins: A Short History." *British Journal of Pharmacology* 147(Suppl 1):S46-S55, 2006. Copyright (c) 2006, Nature Publishing Group (www.nature.com/bjp); Open Access. *British Journal of Pharmacology* Open Access articles are published under the terms of the Creative Commons Attribution License. The CC BY license permits commercial and non-commercial re-use of an open access article as long as the author is properly attributed.

Family	Subtypes	Major effectors	Expression
G$_{12/13}$a	Ga$_{12}$	Phospholipase D (activation)	Ubiquitous
	Ga$_{13}$	Phospholipase Ce (activation)	
		NHE-1 (activation)	
		iNOS (activation)	
		Heat shock protein (HSP) 90 (activation)	
Gb/g	b$_{1-5}$	Adenylyl cyclase I (inhibition)	Most cell types express multiple b and g subtypes
	g$_{1-12}$	Adenylyl cyclases II, IV, VII (activation)	b$_1$g$_1$: retinal rod cells
		GIRK channels (activation)	b$_3$g$_8$: retinal cone cells
		Ca^{2+} (N-, P/Q-, R-type) channels (inhibition)	b$_5$: neurons and neuroendocrine organs
		Phospholipase Cb (activation)	b$_{5(L)}$: retina
		Phosphatidylinositol 3-kinase (activation)	

Note. ERK = extracellular signal-regulated kinase; GIRK = G protein-coupled inwardly rectifying potassium [channel]; iNOS = inducible nitric oxide synthase; MAPK = mitogen-activated protein kinase; Maxi-K$^+$ = large-conductance calcium-activated potassium channel; NHE-1 = sodium-hydrogen antiporter 1.

Source. Adapted from Table 1 (p. S48) in Milligan G, Kostenis E: "Heterotrimeric G-proteins: A Short History." *British Journal of Pharmacology* 147(Suppl 1):S46-S55, 2006. Copyright (c) 2006, Nature Publishing Group (www.nature.com/bjp); Open Access. *British Journal of Pharmacology* Open Access articles are published under the terms of the Creative Commons Attribution License. The CC BY license permits commercial and non-commercial re-use of an open access article as long as the author is properly attributed.

Family	Subtypes	Major effectors	Expression
		Src tyrosine kinase (activation)	
		G protein-coupled receptor kinase recruitment to cell membrane (activation)	

Note. ERK = extracellular signal-regulated kinase; GIRK = G protein-coupled inwardly rectifying potassium [channel]; iNOS = inducible nitric oxide synthase; MAPK = mitogen-activated protein kinase; Maxi-K^+ = large-conductance calcium-activated potassium channel; NHE-1 = sodium-hydrogen antiporter 1.

Source. Adapted from Table 1 (p. S48) in Milligan G, Kostenis E: "Heterotrimeric G-proteins: A Short History." *British Journal of Pharmacology* 147(Suppl 1):S46-S55, 2006. Copyright (c) 2006, Nature Publishing Group (www.nature.com/bjp); Open Access. *British Journal of Pharmacology* Open Access articles are published under the terms of the Creative Commons Attribution License. The CC BY license permits commercial and non-commercial re-use of an open access article as long as the author is properly attributed.

G protein activation cycle. When a GPCR adopts an active conformation, either due to constitutive receptor activity or in response to agonist binding, it initiates a sequence of events leading to G protein activation. At rest, the G protein exists as a heterotrimer, with GDP bound to the guanine nucleotide binding site of the a subunit, which itself is bound to the b/g subunit (Figure 2-5A). Upon agonist binding (Figure 2-5B), the active GPCR conformation allosterically regulates the conformation of the a subunit such that the affinity for GDP decreases and the affinity for GTP increases (Figure 2-5C). This conformation change in the a subunit results in a GDP-to-GTP exchange, wherein GTP replaces GDP in the guanine nucleotide binding domain (Figure 2-5D). In addition, G protein dissociates from the receptor and the b/g subunit dissociates from the GTP-bound a subunit. At this point, the G protein is "active," with GTP bound to the a subunit and the b/g subunit separated from the a subunit, and both separated from the receptor (Figure 2-5E). It should be noted that for some G proteins, activation may involve rearrangement rather than dissociation of the a and b/g subunits (Chung and Wong 2021). The GTP-bound a and the b/g subunits function to regulate their target effector's activity (Figure 2-5F). Activated G proteins can increase or decrease the activity of effectors, depending on the specific characteristics of the G protein. In some cases, the a and b/g subunits co-regulate the activity of the same effector (e.g., adenylyl cyclases and phospholipase Cb). It is generally accepted that a single GPCR in an active conformation can sequentially activate multiple G proteins. This process would contribute to amplification of the signal.

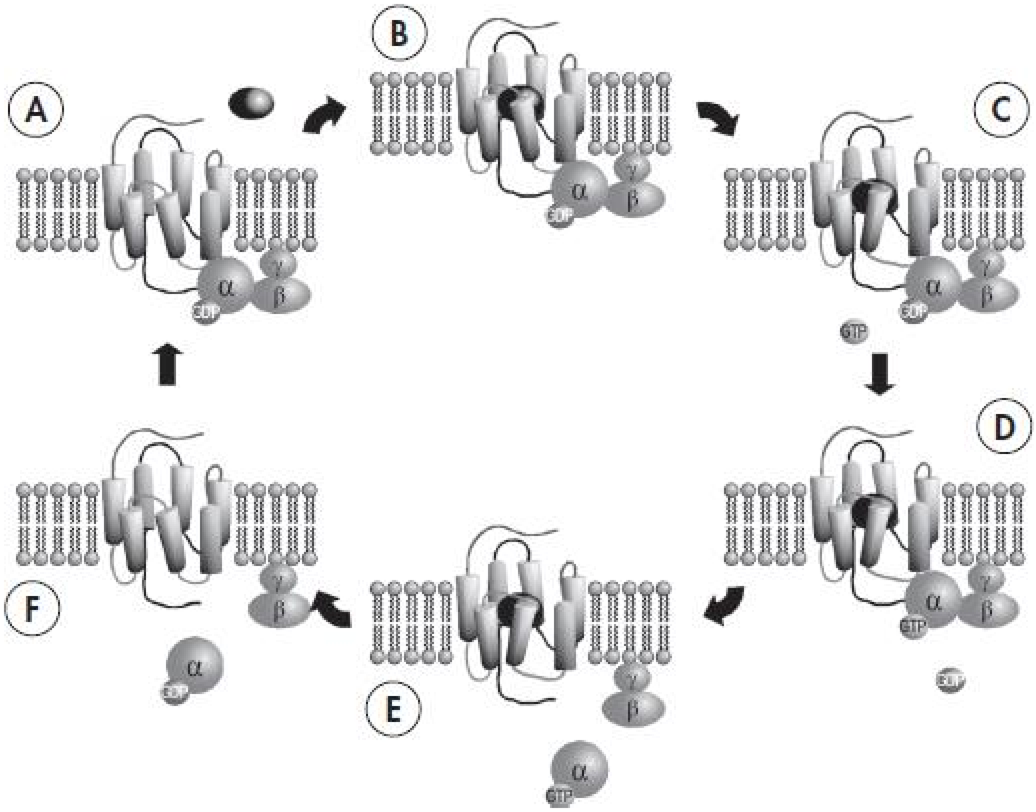


FIGURE 2-5. G protein activation cycle.

See Plate 6 to view this figure in color.

Source. By Sven Jahnichen. Creative Commons Attribution-ShareAlike 3.0 Unported; https://commons.wikimedia.org/w/index.php?curid=730049.

Termination of G protein activity results from the conversion of bound GTP to GDP by the GTPase activity of the a subunit (Figure 2-5F). This enzymatic inactivation process is relatively slow (with turnover rates ranging from 0.1 to 4.0 min$^{[?]1}$, depending on the G protein), which allows time for the regulation of effector activity and further amplification of the signal. For example, a single activated GPCR, signaling through G_s, could result in hundreds of cyclic adenosine monophosphate (cAMP) molecules being formed from increased enzymatic activity of adenylyl cyclase. Upon hydrolysis of GTP to GDP, the inactive a and b/g subunits reform (Figure 2-5A) and can be reactivated if the receptor remains in an active conformation.

Arrestins. In addition to signaling via G proteins, GPCRs can also couple to other cellular transducer molecules to alter cell function. The arrestin family of proteins is perhaps the best studied of these non-G protein transducers. There are four members of the arrestin family (arrestin 1-4). Arrestins 1 and 4 are found primarily in the photoreceptor cells of the retina, whereas the other nonvisual arrestins (2 and 3) are ubiquitously expressed and are also referred to as b-arrestin-1 and b-arrestin-2, respectively. Arrestins bind preferentially to GPCRs in an active conformation, and this interaction changes the conformation of the arrestin molecule, which, by acting as a scaffold, influences the activity of a wide variety of cellular signaling systems (Peterson and Luttrell 2017). Most notably, arrestin signaling activates the mitogen-activated protein kinases (MAPKs) extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38 MAPK, all of which can regulate gene transcription.

Constitutive Receptor Activity

GPCRs can spontaneously adopt an active conformation that can regulate cellular signaling cascades in the absence of an agonist ligand. This process is called *constitutive receptor activity*. As is true for all proteins, GPCRs are not rigid, static structures, but are in constant motion, changing conformations as a result of thermal energy. Given this state of continuous conformational flux, it should come as no surprise that a GPCR can adopt an active conformation. The conformational flexibility of a receptor depends on the number and strength of intramolecular constraints (e.g., bonds, such as hydrogen bonds, van der Waals forces, and electrostatic interactions). Depending on their amino acid sequences, some receptors are more conformationally flexible than others and thus may exhibit higher levels of constitutive activity. At any point in time, some percentage of the receptor population may be in an active, signaling conformation, which contributes to basal cellular activity. It should be noted that the level of constitutive receptor activity is dependent not only on the number of receptors in a population that are active at any point in time but also on the efficiency of receptor-effector coupling, which is strongly influenced by the phenotype of the cell in which the receptor is expressed. For example, for a specific receptor, constitutive receptor activity will be higher in cells with high densities of receptor, transducer, or effector expression, all of which can change with physiological state or disease.

The finding that receptors can signal in the absence of an activating ligand led to the discovery that binding of some ligands can reduce this constitutive activity by stabilizing an inactive conformation (Berg and Clarke 2018). Such ligands are called *inverse agonists* because they have an effect opposite to that of an agonist ligand that stabilizes an active conformation. Thus, in pharmacology we now have five classes of drugs (Figure 2-6): 1) full agonists (which produce maximal effects); 2) partial agonists (which produce less-than-maximal effects); 3) antagonists (which have no to minimal effects of their own but block the effects of agonists); 4) full inverse agonists (which reduce "basal" activity); and 5) partial inverse agonists (which produce less-than-maximal reduction in basal activity). Because constitutive receptor activity depends on cell phenotype, many of the atypical antipsychotic medications that were previously thought to be antagonists have been shown to have inverse agonist properties (Meltzer 2017; Sullivan *et al.* 2015). Although there is considerable optimism about the possible therapeutic benefits of inverse agonists for neuropsychiatric disorders, their clinical utility has yet to be fully realized. As of mid-2023, the FDA has approved only two drugs whose therapeutic efficacy was attributed to inverse agonism. In 2016, the 5-HT$_{2A}$ inverse agonist pimavanserin (Nuplazid) was approved by the FDA for treatment of psychosis associated with Parkinson's disease (Cummings *et al.* 2014).

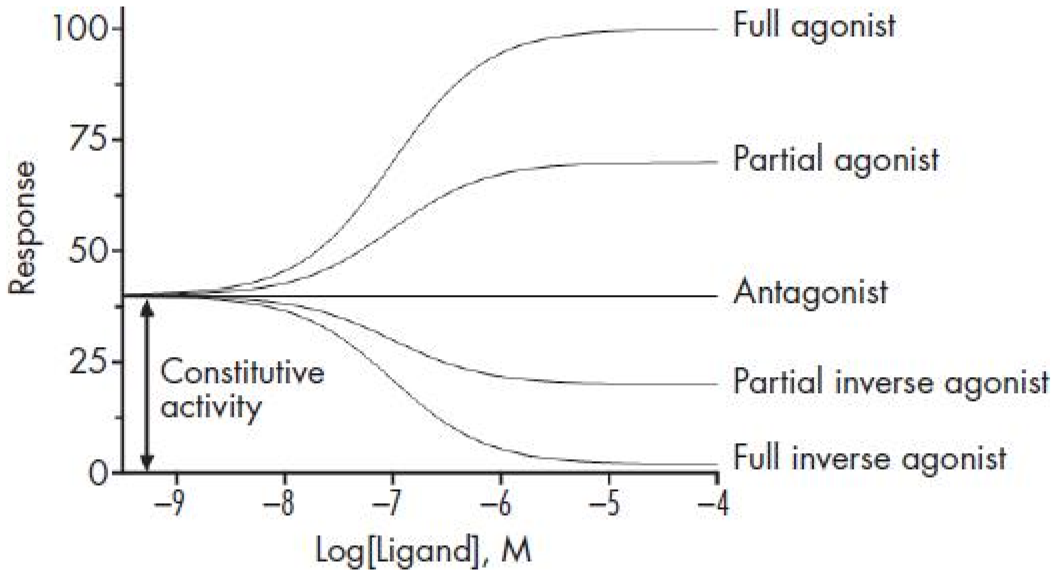


FIGURE 2-6. Pharmacological classes of ligands that act on G protein-coupled receptors.

Source. Adapted from Berg and Clarke 2018.

Functional Selectivity

An important characteristic of GPCRs is that their conformational change can be dependent on the structure of the ligand that binds to them. These ligand-dependent conformations can result in differential, ligand-dependent regulation of various cellular signaling pathways coupled to the receptor. This process is known as *functional selectivity* or *biased agonism* (Berg and Clarke 2018; Kenakin 2021; Urban *et al.* 2007). That drugs can display functional selectivity indicates that drugs have more selectivity than that afforded by differential affinity for different receptor subtypes. Different drugs acting at the same receptor subtype can elicit different cellular responses. For this reason, new drugs may be developed that display better therapeutic efficacy with reduced adverse-effect liability. There are high hopes that ligand-dependent signaling will be of immense value for pharmacotherapy for neuropsychiatric conditions and other diseases. The efficacy of aripiprazole (Abilify) as an antipsychotic medication has been attributed to its functional selectivity at dopamine D_2 and other receptor subtypes (de Bartolomeis *et al.* 2015; Tuplin and Holahan 2017).

Desensitization (homologous and heterologous). Signaling by GPCRs via G proteins to effectors is terminated when the agonist that activated the GPCR dissociates from the receptor and is removed by diffusion or metabolism. However, GPCR signaling can also be terminated/reduced even if the agonist remains bound to the receptor and the receptor remains in an active conformation. This process, wherein GPCR signaling is terminated or reduced with prolonged or repeated agonist exposure, is called *desensitization* or *tachyphylaxis* (Hausdorff *et al.* 1990; Kelly *et al.* 2008; Rajagopal and Shenoy 2018). It should be noted that "prolonged" can mean time periods of seconds to days (Figure 2-7). In addition to that induced by agonist exposure, desensitization can also result from constitutive receptor activity (Berg and Clarke 2018). There are several cellular mechanisms for desensitization. Perhaps the best-studied mechanism involves the binding of an arrestin molecule to the activated receptor. As illustrated in Figure 2-8, following activation, the receptor becomes phosphorylated by G protein receptor kinase (GRK). This phosphorylation increases the affinity for arrestin, resulting in the binding of arrestin to the receptor. Through steric hindrance, arrestin binding interferes with the coupling of G proteins to the receptor, thereby stopping (arresting) G protein signaling. As discussed above (see "Arrestins"), arrestin can also act as a transducer molecule to mediate signaling. In this way, arrestin binding to an activated GPCR can switch signaling from G protein pathways to arrestin-mediated pathways in a time-dependent manner. Because the arrestin molecule also has a clathrin-binding domain, the arrestin-bound receptor becomes associated with clathrin-coated pits in the cell membrane and undergoes internalization, further reducing GPCR activation by extracellular ligands. Internalized receptors can undergo degradation (a process called *downregulation*) or can be dephosphorylated and recycled back to the cell membrane. If receptors are downregulated, recovery of responsiveness requires synthesis of new receptors. Recently, signaling mediated by internalized GPCRs has been reported (Eichel and von Zastrow 2018), which represents an understudied yet highly interesting function of GPCRs that may yield new approaches for therapeutic drug development.

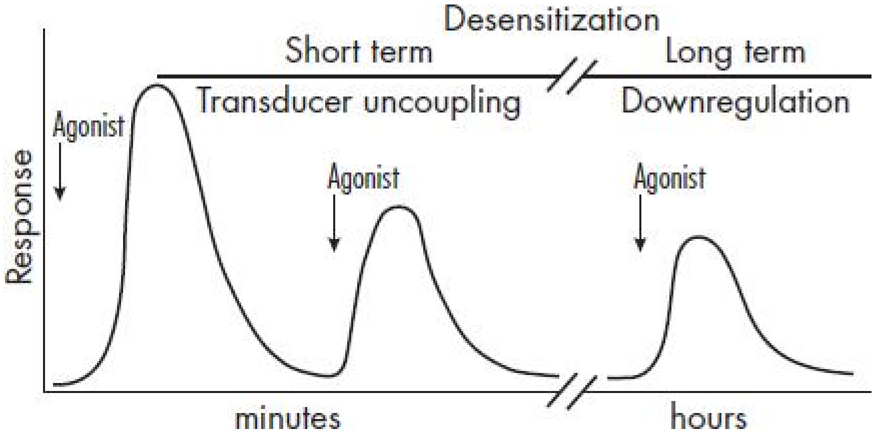


FIGURE 2-7. Time-dependent loss of responsiveness.

Acute and prolonged phases of desensitization: Repeated stimulation with an agonist results in a decreased response over a time frame of minutes (transducer uncoupling or acute desensitization). Over hours to days, repeated stimulation may result in decreased receptor expression at the plasma membrane (downregulation or prolonged desensitization). Together these processes contribute to the phenomenon of tachyphylaxis.

Source. Reprinted from Figure 1 (p. 10) in Rajagopal S, Shenoy SK: "GPCR Desensitization: Acute and Prolonged Phases." *Cellular Signalling* 41:9-16, 2018 (https://doi.org/10.1016/j.cellsig.2017.01.024). Copyright (c) 2018, Elsevier Science Ltd. Used with permission.

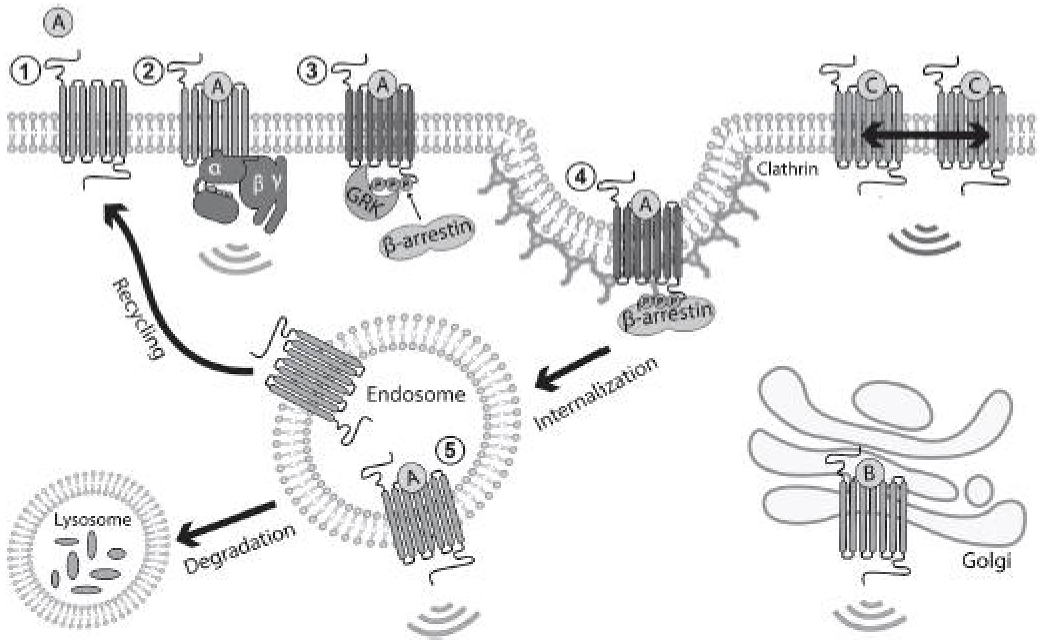


FIGURE 2-8. Agonist-induced signaling and trafficking of opioid receptors.

See Plate 7 to view this figure in color.

Inactive opioid receptors (*gray*) become activated (*green*) after binding to an agonist (drug A; steps 1-2). The active receptor enables signaling via G proteins (*green ripples*, step 2) and triggers phosphorylation of the receptor tail (P) by G protein-coupled receptor kinases (GRKs), followed by receptor engagement of b-arrestins (step 3) and endocytosis via clathrin-coated pits (step 4). These events inactivate G protein signaling (*red receptor*) and ensure signal termination from the plasma membrane by endocytic removal of receptors. After receptors arrive in early endosomes, they have the capacity to signal again by engaging G proteins in the endosome membrane (*green ripples*, step 5). Receptors also engage molecular sorting mechanisms in the endosome limiting membrane (not shown), which determine whether internalized receptors are delivered to lysosomes for proteolytic downregulation or are nondestructively recycled to restore surface receptor responsiveness. Many nonpeptide agonist drugs (drug B) are sufficiently membrane-permeant to activate a discrete pool of opioid receptors at the Golgi apparatus and activate receptors from this location (*green ripples*). Some agonists (drug C) induce receptor reorganization in the plasma membrane to change surface signaling (*blue ripples*).

Source. Reprinted from Figure 1 (p. 426) in Jullie D, Gondin AB, von Zastrow M, Canals M: "Opioid Pharmacology Under the Microscope." *Molecular Pharmacology* 98:425-432, 2020 (https://doi.org/10.1124/mol.119.119321). Copyright (c) 2020, The American Society for Pharmacology and Experimental Therapeutics. Used with permission.

Arrestin-mediated desensitization is an example of *homologous* desensitization, defined as reduced responsiveness of the activated receptor. Homologous desensitization is a negative feedback mechanism that limits the degree of receptor activation. A second type of desensitization is called *heterologous* desensitization, wherein activation of one GPCR alters the responsiveness of a second, different GPCR. Heterologous desensitization often occurs as a result of activation of various kinases, such as protein kinase A (PKA) or protein kinase C (PKC), among others, that are downstream from the first GPCR. These activated kinases can phosphorylate other receptors that contain the proper consensus sequence. Non-GRK-mediated GPCR phosphorylation can also interfere with receptor-transducer-effector coupling and reduce signaling by the phosphorylated receptor. Although activation of non-GRK kinases can mediate heterologous desensitization, these kinases also can participate in negative-feedback, homologous desensitization.

GPCR oligomers. There is substantial evidence to support the existence of functional and dynamic GPCR oligomers, consisting of either GPCR homomers (two or more of the same receptor subtype) or GPCR heteromers (two or more different receptor subtypes). Although GPCR heteromers are well established to occur in heterologous expression systems, evidence for their occurrence in vivo remains somewhat limited. There is also considerable debate over molecular mechanistic issues that underlie the formation of GPCR heteromers, such as whether GPCR heteromer formation is stable or transient (kiss-and-run hypothesis) (Gurevich and Gurevich 2008) and whether ligand binding can induce or stabilize/destabilize heteromer formation (Sierra *et al.* 2020).

The existence of GPCR heteromers greatly increases the number of potential therapeutic targets for the treatment of neuropsychiatric conditions. It has been reported that more than 500 GPCR heteromer pairs have been identified (Borroto-Escuela *et al.* 2014). Notably, GPCR heteromers can have unique signaling, regulatory, and pharmacological

properties and thus are considered by IUPHAR to be distinct receptor entities (Fujita *et al.* 2014). One of the properties of GPCR heteromers that is of great value for pharmacology is interprotomer allosterism. As a result of allosteric interactions between two GPCR protomers of a heteromer, an orthosteric ligand for one of the protomers can act as an allosteric regulator of the affinity, intrinsic efficacy, and/or signaling specificity (i.e., functional selectivity) of an orthosteric ligand for the paired protomer (Figure 2-9). Importantly, these allosteric interactions are ligand-dependent, as is true for all allosteric regulators of GPCRs (Valant *et al.* 2012). Thus, depending on the ligands, an allosteric effect could be facilitatory or inhibitory (antagonistic) or could change cellular signaling specificity for G proteins, b-arrestins, and/or other signaling molecules (Fujita *et al.* 2014; Guitart *et al.* 2014). This ligand dependence increases the opportunities for development of drugs (e.g., bivalent pairs of orthosteric ligands or single ligands with affinity for both protomers) that selectively target heteromers for pharmacotherapy.

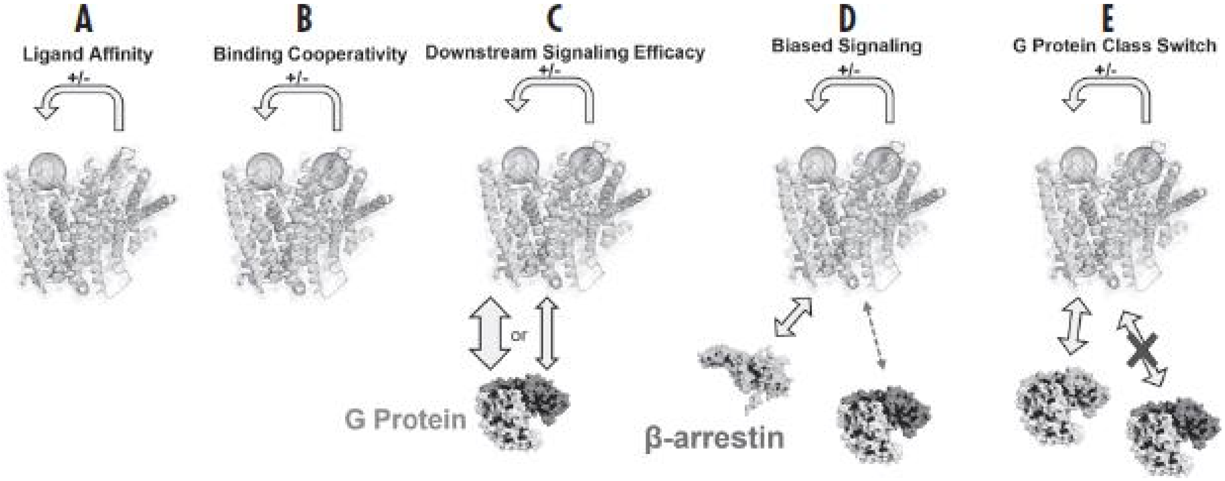


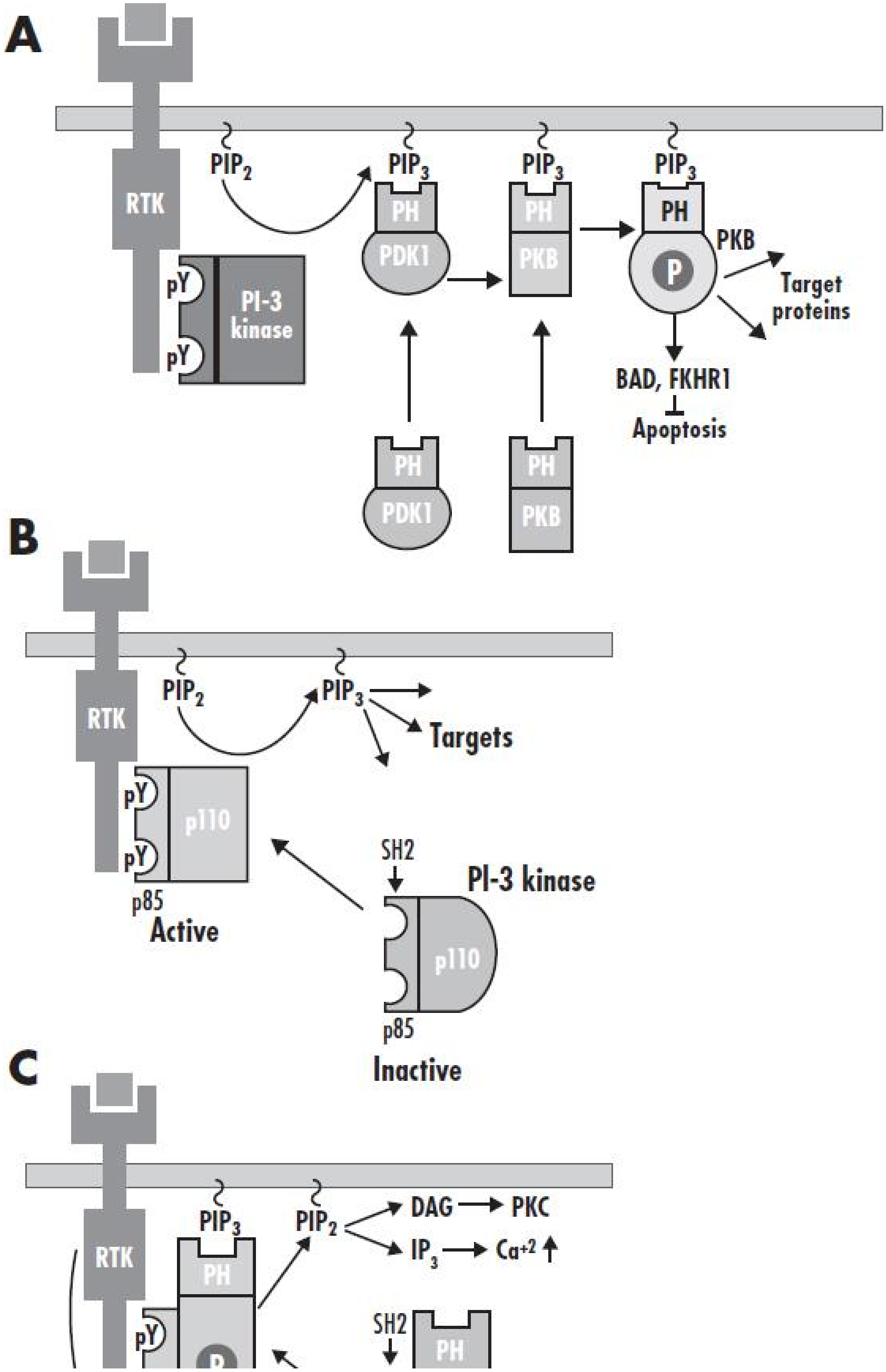
FIGURE 2-9. Models of allosteric interactions between protomers of a heteromer.

See Plate 8 to view this figure in color.

(A) The affinity of a ligand for one protomer (*green*) can be altered by the association of the second protomer (*blue*). **(B)** Binding of an orthosteric ligand to one protomer can alter the affinity of an orthosteric ligand for the second protomer. **(C)** Binding of an orthosteric ligand to one protomer can change the signaling efficiency (intrinsic efficacy) of the orthosteric ligand for the second protomer. Shown is efficiency of coupling to a heterotrimeric G protein, but this extends to other signal-transducing molecules (e.g., b-arrestin). **(D)** Binding of an orthosteric ligand to one protomer can alter the efficiency of coupling of the receptor produced by orthosteric ligand binding to the second protomer to each of multiple transducer molecules (i.e., can alter functional selectivity or agonist bias). Shown are alterations in coupling to a G protein versus b-arrestin. **(E)** Orthosteric ligand binding to one protomer can cause a change in the G protein-coupling specificity produced by the orthosteric ligand for the second protomer (this also changes agonist bias). Shown is a change in coupling efficiency to G proteins with two different a subunits (*light vs. dark blue*).

Source. Modified from Figure 3 (p. 225) in Botta J, Appelhans J, McCormick PJ: "Chapter 7-Continuing Challenges in Targeting Oligomeric GPCR-Based Drugs" (https://doi.org/10.1016/bs.pmbts.2019.11.009), in *Oligomerization in Health and Disease: From Enzymes to G Protein-Coupled Receptors*, Vol 169 (Progress in Molecular Biology and Translational Science book series). Edited by Giraldo J, Ciruela F. Cambridge, MA, Academic Press, 2020, pp. 213-245. Copyright (c) 2020, Elsevier Inc. Used with permission.

Receptor tyrosine kinases. Receptor tyrosine kinases (RTKs) are transmembrane receptors that possess intrinsic enzymatic activity, i.e., cause phosphorylation, as is the case for all kinases. There are 20 different subfamilies of RTKs. They all possess an N-terminal extracellular domain, a single transmembrane domain, and an intracellular kinase domain followed by a C-terminal tail region. The extracellular domains of the subfamilies are divergent, which allows for some degree of ligand specificity. Ligands for these receptors are growth factors such as ephrins, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), epidermal growth factor (EGF), transforming growth factor (TGF), and insulin (Trenker and Jura 2020). Ligand activation leads to dimerization of the receptor accompanied by autophosphorylation, as well as the phosphorylation of tyrosine residues on other signaling molecules (Ullrich and Schlessinger 1990). Such phosphorylation triggers intracellular signal transduction cascades, a very important one being increased activity of the guanosine nucleotide-binding protein Ras, which functions as a small GTPase. Activation of Ras then increases the activity of MAPK, which regulates cell functions such as proliferation, differentiation, mitosis, and apoptosis (Du *et al.* 2005; Simon 2000). In addition to signaling through this pathway, RTKs signal through inositol 1,4,5-trisphosphate (IP$_3$), phospholipase C gamma (PLCg), and Janus kinase/signal transducer activator of transcription (JAK/STAT) (Figure 2-10). There is also increasing evidence for biased agonism for RTKs, as has been established for GPCRs (Karl *et al.* 2020). Given the growth-promoting functions of RTKs, it is not surprising that dysfunction of Ras/MAPK signaling is strongly implicated in the development of many cancers. Such dysfunction has also been implicated in diabetes, severe bone disorders, and arteriosclerosis (Lemmon and Schlessinger 2010; Simon 2000). Changes in RTK signaling have also been hypothesized to be involved in neurological and/or psychiatric disorders (Autry and Monteggia 2012; Duman and Monteggia 2006; Gupta *et al.* 2013; Hashimoto *et al.* 2004).


A
RTK
pY
pY
PI-3 kinase
PIP$_2$
PIP$_3$
PH
PDK1
PIP$_3$
PH
PKB
PIP$_3$
PH
P
PKB
Target proteins
BAD, FKHR1
Apoptosis
PH
PDK1
PH
PKB
B
RTK
PIP$_2$
PIP$_3$
Targets
pY
pY
p110
p85
Active
SH2
PI-3 kinase
p110
p85
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IP$_3$
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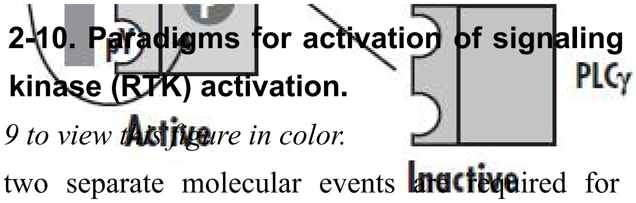


FIGURE 2-10. Paradigms for activation of signaling proteins in response to receptor tyrosine kinase (RTK) activation.

See Plate 9 to view this figure in color.

At least two separate molecular events are required for RTK-induced activation of signaling molecules. Given that many protein targets of RTKs are located at the cell membrane, translocation of RTK to the cell membrane is essential for activation of many effector proteins. **(A) Activation of PKB (also known as Akt) by membrane translocation.** PtdIns(3,4,5)P3 generated in response to growth factor stimulation serves as a binding site for the PH domains of PDK1 and PKB. Membrane translocation is accompanied by release of an autoinhibition leading to activation of PDK1 and PKB kinase activities. Full activation of PKB requires phosphorylation by PDK1 (and also by PDK2). Activated PKB phosphorylates a variety of target proteins that prevent apoptotic death and regulate various metabolic processes. **(B) Activation by a conformational change.** Binding of the SH2 domains of p85, the regulatory subunit of PI-3 kinase, to pTyr sites on activated receptors releases an autoinhibitory constraint that stimulates the catalytic domain (p110). PI-3 kinase catalyzes the phosphorylation of the 39 positions of the inositol ring of PtdIns(4)P and PtdIns(4,5)P2 to generate PtdIns(3,4)P2 and PtdIns(3,4,5)P3, respectively. **(C) Activation by tyrosine phosphorylation.** Binding of the SH2 domains of PLCg to pTyr sites in activated receptors facilitates tyrosine phosphorylation of PLCg as well as membrane translocation, a process mediated in part by binding of the PH domain to PI-3 kinase products. Tyrosine phosphorylation is essential for PLCg activation, leading to hydrolysis of PtdIns(4,5)P2 and generation of the two second messengers Ins(1,4,5)P3 and diacyglycosol. BAD = Bcl-2 agonist of cell death; DAG = diacylglycerol; FKHR1 = winged helix transcription factor; Ins (1,4,5)P3 = inositol 1,4,5-trisphosphate; IP_3 = inositol 1,4,5-trisphosphate; p110 = catalytic subunit of PI-3 kinase; p85 = regulatory subunit of PI-3 kinase; PDK1 = pyruvate dehydrogenase kinase isoform 1; PDK2 = pyruvate dehydrogenase kinase isoform 2; PH = Pleckstrin homology; PI = phosphatidylinositol; PI-3 kinase = phosphatidylinositol-3 kinase; PIP_2 = phosphatidylinositol (4,5)-bisphosphate; PIP_3 = phosphatidylinositol (3,4,5)-trisphosphate; PKB = protein kinase B; PKC = protein kinase C; PLCg = phospholipase C gamma; PtdIns(3,4)P2 = phosphatidylinositol-bisphosphate; PtdIns(3,4,5)P3 = phosphatidylinositol (3,4,5)-trisphosphate; PtdIns(4)P = phosphatidylinositol-4-phosphate; PtdIns(4,5)P2 = phosphatidylinositol 4,5-bisphosphate; pY = phosphorylated tyrosine residue; pTyr = phosphotyrosine; SH2 = Src homology 2.

Source. Reprinted from Figure 4 (p. 216) in Schlessinger J: "Cell Signaling by Receptor Tyrosine Kinases." *Cell* 103(2):211-225, 2000 (https://doi.org/10.1016/S0092-8674(00)00114-8). Copyright (c) 2000, Cell Press. Used with permission.

In the developing brain, RTKs promote neuronal differentiation and axon targeting; however, in the adult brain, RTKs regulate structural and synaptic plasticity (Chao 2003). Consequently, RTKs are thought to play a role in learning and memory. In particular, BDNF may serve as a mediator rather than a modulator of synaptic plasticity and communication (Johnstone and Mobley 2020; Park and Poo 2013). Interfering with BDNF signaling, possibly by targeting its receptor, TrkB, is a developing strategy for treatments for neurological or psychiatric disorders, including alcohol use disorder (Autry and Monteggia 2012; Gupta *et al.* 2013; Hamada and Lasek 2020; Nagahara and Tuszynski 2011). The involvement of BDNF/TrkB signaling in the antidepressant effect of ketamine (Carreno *et al.* 2020; Duman and Monteggia 2006; Kavalali and Monteggia 2020; Yang *et al.* 2019) gives further credence to a role for RTKs in the mechanism of action of psychotherapeutic drugs. Of course, the widespread growth and synaptic effects of BDNF raise important caveats for therapies targeting BDNF signaling.

Neurotransmitter and Neuropeptide Systems

Serotonergic System

Serotonin was first synthesized by Maurice Rapport in 1948 after he identified it as a vasoconstrictor substance in blood (Rapport *et al.* 1948). Later, it was found that serotonin was the same molecule, previously called enteramine, isolated from chromaffin cells of the intestinal muscosa by Erspamer (1937) in 1935. Most of the serotonin in the body is found outside the CNS, in enterochromaffin cells of the gastrointestinal system (90%) and in platelets (8%) (Gershon 2013). Although 5-HT plays a vital role in the regulation of a wide variety of CNS functions, only about 1%-2% of serotonin is found in the CNS. Serotonin is an indolealkyl amine (see Figure 2-1). Even though serotonergic cells represent only a small percentage of neurons in the brain (~0.0001%), serotonergic neurons have an enormous influence on other neurons in brain. It has been estimated that each cortical target neuron receives approximately 200 contacts by serotonergic neurons (Jacobs and Azmitia 1992). Because of serotonin's key role in the regulation of mood and affective states, finding ways to modify and stabilize serotonin neuron activity and function has been a major ongoing focus of psychiatric disorder research and pharmacotherapy.

An excess of serotonin receptor activation, produced by high dosages or combinations of certain drugs--such as selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), cocaine, and various serotonergic agonists (buspirone, triptans, L-tryptophan, amphetamine derivatives, 3,4-methylenedioxymethamphetamine [MDMA, "Ecstasy"])--can cause a variety of effects collectively known as the *serotonin syndrome* (Simon and Keenaghan 2021). In humans, symptoms of serotonin syndrome (which can be life-threatening) include altered mental status, autonomic dysfunction (hyperthermia, high blood pressure, tachycardia, pupil dilation), and neuromuscular excitation (e.g., tremor, hypertonia, hyperreflexia). A serotonin syndrome can also occur in animals, characterized by tremor, ataxia, loss of plantar reflex, gastrointestinal effects, pupil dilatation, piloerection, and increased motor activity (Haberzettl *et al.* 2013). In rats and mice, the characteristic behaviors observed include forepaw treading, resting tremor, rigidity, Straub tail, hind limb abduction, and head weaving.

5-HT neurons project widely throughout the CNS and innervate virtually every part of the neuroaxis (Figure 2-11A). Serotonin is synthesized from the essential amino acid L-tryptophan. L-tryptophan undergoes hydroxylation at the 5-position of the ring by a rate-limiting enzyme, tryptophan hydroxylase, to form 5-hydroxytryptophan (5-HTP). 5-HTP is converted to 5-HT by the enzyme aromatic L-amino acid decarboxylase (AADC). In neurons, 5-HT is stored at high concentrations in vesicles by the action of a vesicular monoamine transporter (VMAT), which is discussed in more detail below. Upon activation of raphe serotonergic neurons, depolarization of the neuron terminals by invasion of action potentials promotes fusion of serotonin-containing vesicles to the membrane and extracellular release of serotonin (Figure 2-11B). In addition to being released at the synapse, serotonin can be released extrasynaptically from cell bodies, dendrites, and axons (Quentin *et al.* 2018). This type of extrasynaptic release, termed *volume transmission*, has slow kinetics and influences a larger area than that influenced by synaptic release. The impact of these two modes of neurotransmission on pathophysiological functions, behaviors, and pharmacotherapy is not yet clear.

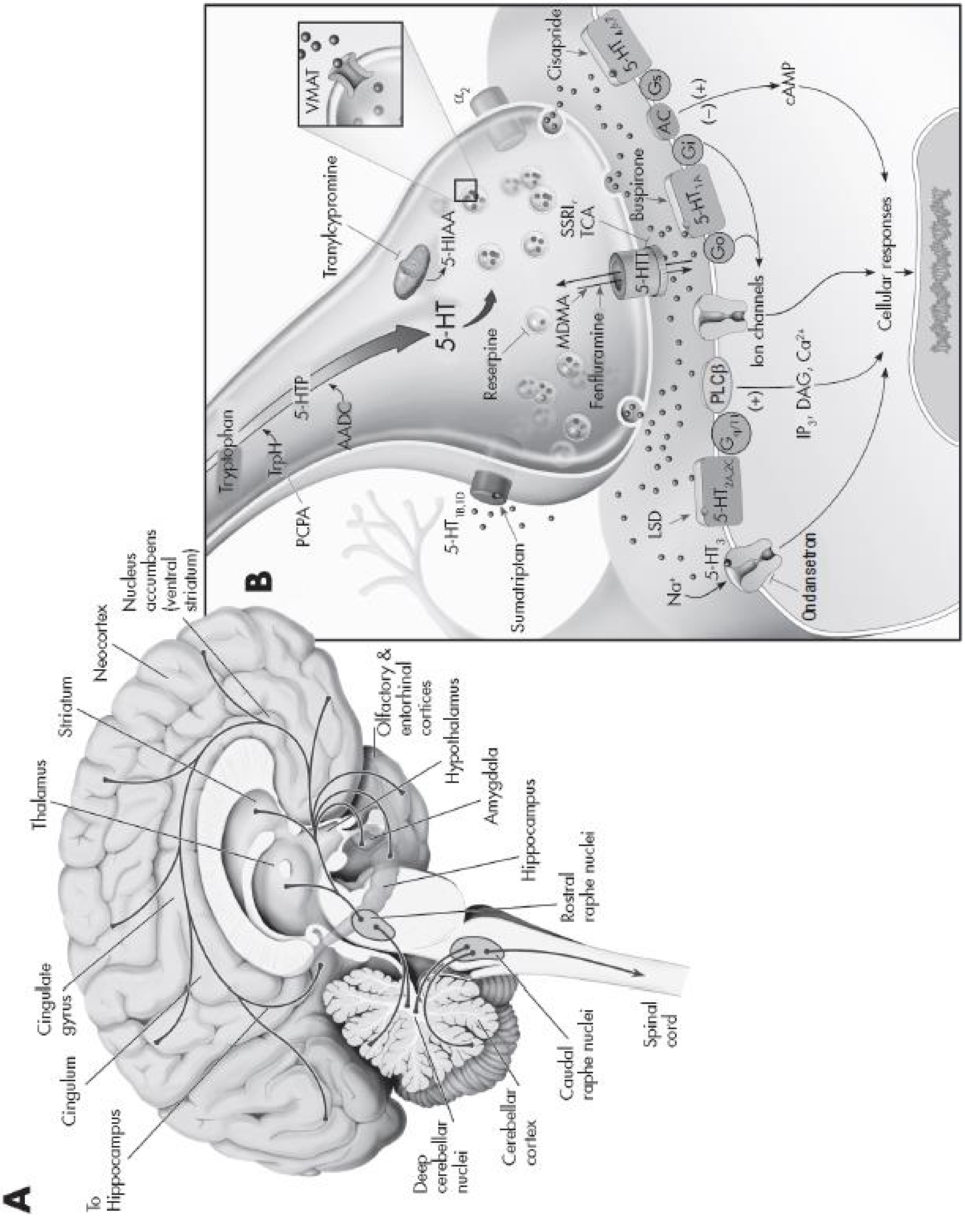

A
To Hippocampus
Cingulum
Cingulate gyrus
Thalamus
Striatum
Neocortex
Nucleus accumbens (ventral striatum)
Olfactory & entorhinal cortices
Hypothalamus
Amygdala
Hippocampus
Rostral raphe nuclei
Caudal raphe nuclei
Spinal cord
Cerebellar cortex
Deep cerebellar nuclei
B
Tryptophan
TrpH
PCPA
5-HTP
AADC
5-HT
Tranylcypromine
5-HIAA
VMAT
α_2
Reserpine
MDMA
Fenfluramine
SSRI, TCA
5-HTT
Buspirone
Cisapride
$5\text{-HT}_{1B,1D}$
Sumatriptan
LSD
$5\text{-HT}_{2A,2C}$
$G_{q/11}$
PLCβ
(+)
IP_3, DAG, Ca^{2+}
Ion channels
Go
5-HT_{1A}
Gi
AC
Gs
$5\text{-HT}_{4,6,7}$
(−)
(+)
cAMP
Cellular responses
Na^+
5-HT_3
Ondansetron

FIGURE 2-11. The serotonergic system.

See Plate 10 to view this figure in color.

(A) Location of the major serotonin (5-hydroxytryptamine [5-HT])-producing cells (raphe nuclei) innervating brain structures. **(B)** Various cellular regulatory processes involved in serotonergic neurotransmission and sites of action of drugs affecting serotonergic transmission. *L-Tryptophan*, the precursor for 5-HT, is converted to 5-hydroxytryptophan (5-HTP) by the rate-limiting enzyme tryptophan hydroxylase (TrpH). Aromatic L-amino acid decarboxylase (*AADC*) then converts 5-HTP to 5-HT. Once released from the presynaptic terminal, 5-HT can interact with a variety (14 different types) of presynaptic and postsynaptic receptors. *Sumatriptan*, a 5-$HT_{1B,1D}$ receptor agonist, has antimigraine effects that are thought to be due to activation of $HT_{1B,1D}$ receptors expressed on smooth muscle (to produce vasoconstriction) and also on pain-sensing neurons (i.e., *nociceptors*) (to reduce the release of pain-related neuropeptides). *Buspirone* is a partial 5-HT_{1A} receptor agonist that activates both pre-and postsynaptic receptors. *Cisapride* is a preferential 5-HT_4 receptor agonist that is used to treat irritable bowel syndrome as well as nausea associated with antidepressants. Binding of 5-HT to G protein-coupled receptors (GPCRs) that are coupled to adenylyl cyclase (AC) and phospholipase C beta (PLCb) will result in production of a cascade of second-messenger and cellular effects. Lysergic acid diethylamide (*LSD*) likely interacts with numerous 5-HT receptors to mediate its effects. Pharmacologically, this ligand is often used as a 5-HT_2 receptor agonist in receptor-binding experiments. *Ondansetron* is a 5-HT_3 receptor antagonist that is marketed as an antiemetic agent for chemotherapy patients but is also given to counteract side effects produced by antidepressants in some patients. 5-HT has its action terminated by being taken back into the presynaptic neuron through 5-HT transporters (5-HTTs [also called SERTs]). (Note that 5-HTTs are located extrasynaptically, not synaptically [as depicted in figure].) Once inside the neuron, 5-HT can either be repackaged into vesicles for reuse or undergo enzymatic catabolism. The selective serotonin reuptake inhibitors (*SSRIs*) and older-generation tricyclic antidepressants (*TCAs*) are able to interfere with or block the reuptake of 5-HT. 5-HT is metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase (MAO), located on the outer membrane of mitochondria or sequestered and stored in secretory vesicles by vesicular monoamine transporters (VMATs). *Reserpine* causes a depletion of 5-HT in vesicles by interfering with uptake and storage mechanisms (depressive-like symptoms have been reported with this agent). *Tranylcypromine* is an MAO inhibitor (MAOI) and an effective antidepressant. *Fenfluramine* (an anorectic agent) and 3,4-methylenedioxymethamphetamine (*MDMA*; "Ecstasy") are able to facilitate 5-HT release by altering SERT function. cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; IP_3 = inositol 1,4,5-triphosphate.

Source. Reprinted from Figure 2-3 (pp. 56-57) in Drazinic CM, Szabo ST, Gould TD, Manji HK: "Neurotransmitters and Receptors in Psychiatric Disorders," in *The American Psychiatric Association Textbook of Psychopharmacology*, 5th Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Association Publishing, 2017, pp. 45-116. Copyright (c) 2017, American Psychiatric Association. Used with permission.

Once released, serotonin can act on receptors (discussed below) located on postsynaptic cells (heteroreceptors) and on the serotonergic neurons themselves (presynaptic receptors, autoreceptors). Autoreceptors on serotonergic neurons can be found on cell bodies (somatodendritic autoreceptors) and on neuron terminals (terminal autoreceptors). Serotonergic somatodendritic autoreceptors are composed of the 5-HT$_{1A}$ subtype (which also can be found on postsynaptic neurons) and function to decrease the firing rate of the serotonergic neurons. Autoreceptors on the serotonin neuron terminals are of the 5-HT$_{1B}$ subtype (which also can be found on postsynaptic neurons) and function to decrease the release of serotonin from the activated neuron. In these ways (i.e., via reduced cell firing and reduced serotonin release), serotonergic autoreceptors mediate negative feedback to regulate the activity of serotonergic neurons.

Serotonin's actions are terminated by rapid uptake back into serotonergic neurons, a process mediated by serotonin transporters (see "Serotonin Transporters" below). Once back inside the cell, serotonin can be repackaged into vesicles (via VMAT2) or enzymatically degraded by monoamine oxidase (MAO), located on the outer membrane of mitochondria, to 5-hydroxyindoleacetic acid (5-HIAA). 5-HIAA levels in cerebrospinal fluid provide an index of serotonin levels in the CNS, whereas 5-HIAA levels in urine provide an index of peripheral serotonin levels and are diagnostic for the presence of carcinoid tumors of enterochromaffin cells.

The importance of serotonin in the CNS has been demonstrated through use of pharmacological tools. Destruction of serotonergic neurons with neurotoxins (e.g., *para*-chloroamphetamine [pCA] or 5,7-dihydroxytryptamine [5,7-DHT]) or with electrolytic lesions of the raphe nuclei, or depletion of serotonin with inhibitors of synthesis (e.g., *para*-chlorophenylalanine [pCPA]) or inhibitors of VMAT (e.g., reserpine) produces a variety of behavioral changes in animals (e.g., nonaggression, hypersexuality, hyperlocomotion). Dietary restriction of the essential amino acid tryptophan in humans can cause a resurgence of depressive symptoms in patients treated successfully with SSRIs (see below) (Salomon *et al.*

1993). Conversely, inhibition of serotonin metabolism via inhibition of MAO can lead to improved mood--and in fact, MAOIs are antidepressant drugs (Culpepper 2012).

Serotonin Receptors

Serotonin acts on a large variety of receptors in the CNS to regulate numerous physiological functions and behaviors. The history of serotonin receptor nomenclature is quite complex (for an excellent review, see Barnes *et al.* 2021) starting in 1957 with the identification of two serotonin receptor subtypes by Gaddum and Picarelli (1957). There are 14 receptor subtypes distributed into seven families. With the exception of 5-HT_3 receptors, which are ligand-gated ion channels, all of the serotonin receptors are GPCRs (Table 2-2).

TABLE 2-2. Nomenclature for serotonin (5-hydroxytryptamine; 5-HT) receptors

5-HT receptor groups	Nomenclature for 5-HT receptors in the group	Comments
5-HT_1 receptors	5-HT_{1A} receptor	
	5-HT_{1B} receptor	
	5-HT_{1D} receptor	
	5-ht_{1e} receptor	Lowercase appellation used by convention because a functional response in native cells or tissues has not been identified.
	5-HT_{1F} receptor	

Source. Reprinted from Table 1 (p. 319) in Barnes NM, Ahern GP, Becamel C, et al.: "International Union of Basic and Clinical Pharmacology. Cx. Classification of Receptors for 5-Hydroxytryptamine; Pharmacology and Function." *Pharmacological Reviews* 73(1):310-520, 2021 (https://doi.org/10.1124/pr.118.015552). Copyright (c) 2020 by The American Society for Pharmacology and Experimental Therapeutics. Used with permission.

5-HT receptor groups	Nomenclature for 5-HT receptors in the group	Comments
5-HT$_2$ receptors	5-HT$_{2A}$ receptor	
	5-HT$_{2B}$ receptor	
	5-HT$_{2C}$ receptor	
5-HT$_3$ receptors	Native receptors of unknown stoichiometry:	Five known subunits: 5-HT$_{3A}$, 5-HT$_{3B}$, 5-HT$_{3C}$, 5-HT$_{3D}$, and 5-HT$_{3E}$
	5-HT$_3$ receptor	5-HT$_3$ receptors are pentameric complexes with the presence of 5-HT$_{3A}$ subunits a prerequisite for function; i.e., only the homomeric 5-HT$_{3A}$ receptor is functional. Heteromeric 5-HT$_3$ receptors are likely to require at least two 5-HT$_{3A}$ subunits.
	Heterologous expression of known subunits such as	
	Homomeric receptor:	
	5-HT$_{3A}$ receptor	
	Heteromeric receptor:	
	5-HT$_{3AB}$ receptor	
	5-HT$_{3AC}$ receptor	
5-HT$_4$ receptor		

Source. Reprinted from Table 1 (p. 319) in Barnes NM, Ahern GP, Becamel C, et al.: "International Union of Basic and Clinical Pharmacology. Cx. Classification of Receptors for 5-Hydroxytryptamine; Pharmacology and Function." *Pharmacological Reviews* 73(1):310-520, 2021 (https://doi.org/10.1124/pr.118.015552). Copyright (c) 2020 by The American Society for Pharmacology and Experimental Therapeutics. Used with permission.

5-HT receptor groups	**Nomenclature for 5-HT receptors in the group**	**Comments**
5-HT$_5$ receptors	5-HT$_{5A}$ receptor	
	5-ht$_{5b}$ receptor	Lowercase appellation used by convention because a functional response in native cells or tissues has not been identified.
5-HT$_6$ receptor		
5-HT$_7$ receptor		

Source. Reprinted from Table 1 (p. 319) in Barnes NM, Ahern GP, Becamel C, et al.: "International Union of Basic and Clinical Pharmacology. Cx. Classification of Receptors for 5-Hydroxytryptamine; Pharmacology and Function." *Pharmacological Reviews* 73(1):310-520, 2021 (https://doi.org/10.1124/pr.118.015552). Copyright (c) 2020 by The American Society for Pharmacology and Experimental Therapeutics. Used with permission.

The serotonin type 1 receptor subfamily consists of 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1e}$, and 5-HT$_{1F}$ subtypes, which share 40%-60% of their sequence identity. These receptors are best known to couple to the G$_{i/o}$ family of G proteins (although not exclusively), leading to inhibition of adenylyl cyclase activity, activation of G protein-coupled inwardly rectifying potassium (GIRK) channels, and inhibition of calcium channels in neurons. Although originally defined as a member of the 5-HT$_1$ subfamily, the 5-HT$_{1C}$ receptor was later recharacterized as the 5-HT$_{2C}$ receptor on the basis of its structural and functional similarity to the 5-HT$_2$ subfamily.

5-HT_{1A} receptors are distributed widely throughout the CNS, notably in limbic regions, consistent with these receptors' prominent role in neuropsychiatric disease, including major depressive disorder, anxiety disorders, and schizophrenia (Celada *et al.* 2013). A role for 5-HT_{1A} receptors has been indicated in a variety of other conditions, such as cognitive impairment, pain, fear, substance use disorders, Parkinson's disease, female sexual dysfunction, and respiratory dysfunction. Although a variety of clinically used drugs are known to directly target 5-HT_{1A} receptors (e.g., buspirone, clozapine, ziprasidone, aripiprazole, vilazodone), there are no FDA-approved drugs that selectively target the 5-HT_{1A} receptor. Additionally, the 5-HT_{1A} receptor is involved in the mechanism of antidepressant action of a variety of drugs (Richardson-Jones *et al.* 2010; Samuels *et al.* 2016) that act to increase serotonin levels, including SSRIs, MAOIs, and tricyclic antidepressants (TCAs), although it should be noted that many receptors have been found to play a role in the action of these drug classes. Development

of selective ligands that target the 5-HT_{1A} receptor will likely be of value in the treatment of mood disorders.

In addition to being postsynaptic receptors, 5-HT_{1A} receptors are also located on the soma and dendrites of serotonergic neurons in the raphe nuclei (somatodendritic autoreceptors). These receptors participate in negative-feedback regulation of serotonergic neurons, as their activation by serotonin released by activated serotonergic neurons inhibits the firing of serotonergic neurons, resulting in decreased serotonin release. Desensitization of these somatodendritic autoreceptors has been found to play a role in the mechanism of action of SSRIs (Artigas *et al.* 2006; Millan 2006), and

small interfering RNA (siRNA)-induced knockdown of 5-HT_{1A} receptors produces robust antidepressant-like effects in mice. By contrast, activation of 5-HT_{1A} autoreceptors produces anxiolytic behaviors in rodents (De Vry *et al.* 2004).

As is the case for 5-HT_{1A} receptors, 5-HT_{1B} receptors are expressed both postsynaptically and presynaptically on serotonergic neurons. However, 5-HT_{1B} autoreceptors are expressed on terminals of serotonergic neurons located in various target areas throughout the CNS. Activation of terminal 5-HT_{1B} receptors reduces release of serotonin from activated neurons, thereby participating in negative-feedback regulation of serotonin release. The 5-HT_{1B} receptor plays a role in depression and anxiety behaviors as well as in aggression and impulsivity. Whereas presynaptic 5-HT_{1B} autoreceptors appear to be involved in depression and anxiety in mice (Nautiyal *et al.* 2016), postsynaptic 5-HT_{1B} receptors regulate aggressive behavior and impulse control (Nautiyal *et al.* 2015). However, studies of the function of 5-HT_{1B} receptors have been complicated by both pharmacological differences across species and similarity to the 5-HT_{1D} receptor, although the expression level of the 5-HT_{1B} receptor is much higher than that of the 5-HT_{1D} receptor. With a lack of selective ligands, identification of distinct functional roles of these two receptor subtypes remains a challenge. For a discussion of the rather confusing history of the nomenclature regarding the 5-HT_{1B} and 5-HT_{1D} receptors, see the excellent review by Barnes *et al.* (2021). Currently, there are no drugs available that can selectively target pre-versus postsynaptic 5-HT_{1B} receptors.

5-HT_{1B} receptors, along with 5-HT_{1D} and 5-HT_{1F} receptors, are targets for the triptan class of drugs (e.g., sumatriptan, zolmitriptan, naratriptan, rizatriptan) that are used to treat migraine. Initially, the antimigraine efficacy of the triptans was attributed to agonist action at the 5-HT_{1B} receptor to promote vasoconstriction in arteries in the brain (Goadsby *et al.* 2017). However, the 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors are also located on sensory neurons that mediate pain neurotransmission. Activation of these receptors inhibits pain-sensing neuron (nociceptor) release of the neuropeptide calcitonin gene-related peptide (CGRP), thereby reducing pain neurotransmission. Thus, inhibition of pain-sensing neurons that innervate the meninges of the CNS by activation of 5-HT_{1B}, 5-HT_{1D}, and/or

5-HT_{1F} receptors is thought to be the primary therapeutic mechanism of the triptans (Goadsby *et al.* 2017). Notably, agonists selective for the 5-HT_{1F} receptor have been developed that are effective in the acute treatment of migraine pain. In 2019, the 5-HT_{1F} agonist lasmiditan was approved for use in the treatment of migraine (Kuca *et al.* 2018).

The 5-HT_2 family consists of three members, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The 5-HT_{2A} and 5-HT_{2C} receptors share significant sequence homology, making the development of selective ligands difficult. Many antagonists initially developed for the 5-HT_{2A} receptor are now known to bind to the 5-HT_{2C} receptor. The canonical signaling pathway for all three of these receptors is the $G_{q/11}$ family of G proteins, which activates phospholipase C to produce two second messengers derived from hydrolysis of inositol 4,5-bisphosphate: 1) diacylglycerol, which activates protein kinase C (PKC), and 2) inositol 1,4,5-trisphosphate (IP_3), which mobilizes intracellular calcium from the endoplasmic reticulum. Activation of these signaling pathways influences a great many cellular processes and is generally excitatory in neurons, in contrast to the inhibitory actions of the 5-HT_1 receptors. However, as is the case for all GPCRs, signaling by 5-HT_2 receptors is not restricted to the most studied, canonical signaling pathway. Coupling of 5-HT_2 receptors to multiple G proteins (such as G_i) as well as

to G protein-independent pathways has been demonstrated (for a review, see Barnes *et al.* 2021).

The 5-HT_{2A} receptor can be found both in the CNS and in the periphery. It is especially prominent in vascular smooth muscle, where it is involved in regulation of the contractile state. In the CNS, 5-HT_{2A} receptors are widely distributed but are found especially in cortical and limbic areas.

The 5-HT_{2A} receptor is perhaps best known as a central target for hallucinogenic drugs, such as lysergic acid diethylamide (LSD), *N,N*-dimethyltryptamine (DMT), and psilocybin (Nichols 2016). Although there was evidence from studies before 1970 that serotonergic hallucinogens were markedly effective in treating various neuropsychiatric conditions (e.g., obsessive-compulsive disorder [OCD], substance use disorders [alcohol, nicotine, opioid], anxiety, depression), clinical research of these substances was curtailed when LSD was placed in Schedule I of the 1970 Controlled Substances Act, largely because of its popularity as a recreational drug. Fortunately, research has resumed, and there is now evidence that acute exposure to these classical psychedelic drugs, under controlled, supportive environmental conditions, is highly effective in treating depression (in cancer patients, in individuals with treatment-resistant depression, and in persons with substance use disorders (Johnson *et al.* 2019). The FDA granted "breakthrough therapy" status to psilocybin in 2018 for use in clinical trials for treatment-resistant depression (Carhart-Harris *et al.* 2021) and in 2019 for use in clinical trials for major depressive disorder (Davis *et al.* 2021).

The 5-HT_{2A} receptor is also an important target for atypical antipsychotics in the treatment of schizophrenia (Kantrowitz 2020). The first-generation (also known as "conventional") antipsychotics were largely dopamine D_2 receptor antagonists (e.g., haloperidol), and although they were effective in diminishing psychosis, they were associated with serious adverse extrapyramidal side effects (EPS). The second-generation (also known as "atypical") antipsychotics (e.g., clozapine, risperidone, olanzapine, paliperidone, lumateperone) have reduced affinity for dopamine D_2 receptors, greater 5-HT_{2A} receptor antagonism, and lower risk of EPS, albeit with increased liability for weight gain and metabolic syndrome. Although the 5-HT_{2A} receptor plays a central role in the reduced adverse EPS of the atypical antipsychotics, it does not appear to be essential for efficacy in treatment of psychotic symptoms. It should be noted that in addition to dopamine D_2 and 5-HT_{2A} receptors, atypical antipsychotics have affinity for a variety of receptor subtypes (e.g., the 5-HT_{2C} receptor), which may be important in their mechanism of action (Meltzer 2017). Given the multifaceted complexity of neuropsychiatric disorders such as schizophrenia, it should not be surprising that an effective treatment strategy may require targeting multiple receptor systems with nonselective drugs (i.e., a "magic shotgun" versus a "magic bullet" approach [Roth *et al.* 2004]).

Although 5-HT$_{2A}$ antagonism does not appear to play a substantive role in the mechanism of action of atypical antipsychotics, the 5-HT$_{2A}$ antagonist pimavanserin was approved by the FDA in 2016 for treatment of psychosis associated with Parkinson's disease. The purported mechanism of pimavanserin's antipsychotic efficacy is 5-HT$_{2A}$ receptor inverse agonism (i.e., reduction of constitutive receptor activity). Pimavanserin also has inverse agonist efficacy at the 5-HT$_{2C}$ receptor; however, it does not have appreciable affinity at dopaminergic receptors. Whether the difference in antipsychotic efficacy of pimavanserin versus that of the atypical antipsychotics is due to inverse agonism versus antagonism is not clear (Nutt *et al.* 2017). Furthermore, pimavanserin's inverse agonism has been demonstrated only in vitro, in heterologous expression systems. Caution must be exercised in extrapolating in vitro effects to in vivo mechanisms of action, given that constitutive receptor activity and inverse agonism are dependent on cell phenotype and physiological state (Berg and Clarke 2018).

The 5-HT$_{2B}$ receptor was first identified in the fundus of the rat stomach and in the periphery and is involved in regulation of gastrointestinal, cardiac, vascular, and pulmonary functions. There have been relatively few studies of this receptor's role in the CNS. Although there are currently no clinically available drugs that selectively target the 5-HT$_{2B}$ receptor, a strong case for development of compounds that target the 5-HT$_{2B}$ receptor has been made on the basis of studies demonstrating 5-HT$_{2B}$ receptor-mediated regulation of serotonergic and dopaminergic neuronal activity (Devroye *et al.* 2018). However, in view of reports that drugs with agonism at 5-HT$_{2B}$ receptors can produce lethal cardiac valvulopathies and pulmonary hypertension (an effect that caused drugs such as fenfluramine, pergolide, and cabergoline to be withdrawn from the market), development of 5-HT$_{2B}$-targeting drugs must proceed with caution.

Although the 5-HT$_{2C}$ receptor is expressed throughout the brain, its expression level is much lower than that of the 5-HT$_{2A}$ receptor, except in the choroid plexus. The messenger RNA (mRNA) for the 5-HT$_{2C}$ receptor is the only GPCR found to date that undergoes a posttranscriptional process called mRNA editing, which changes the amino acid sequence of three amino acids in the second intracellular loop. As a result of this change in sequence, there are 14 different isoforms of the 5-HT$_{2C}$ receptor that can be expressed in humans. Changes to the amino acid sequence in the second intracellular loop due to mRNA editing result in changes in the receptor's ability to couple to G proteins and can also change the receptor's signaling specificity. mRNA editing is a regulated phenomenon in cells; thus, the pattern of 5-HT$_{2C}$ receptor isoform expression--and subsequently 5-HT$_{2C}$ receptor function--is subject to change with cell phenotype and physiological state. While it is clear that 5-HT$_{2C}$ mRNA editing markedly alters 5-HT$_{2C}$ receptor function (Olaghere da Silva *et al.* 2010), the consequences of these changes for pathophysiology and therapeutics are currently unknown.

Consistent with this receptor's wide distribution in the brain, activation of the 5-HT$_{2C}$ receptor leads to a variety of behavioral responses in rodents, including anxiety, hypolocomotion, hyperthermia, hypophagia, and penile erection. Importantly for therapeutics, the 5-HT$_{2C}$ receptor has been shown to regulate compulsive drug-and food-seeking behaviors, energy homeostasis, mood and cognition disorders, and seizures (Di Giovanni and De Deurwaerdere 2016), suggesting that 5-HT$_{2C}$ ligands may be effective in treating substance-related and addictive disorders (Collins *et al.* 2018) as well as other neuropsychiatric conditions (Palacios *et al.* 2017).

Many reports have shown that selective 5-HT$_{2C}$ agonists reduce food intake, which led to optimism that a compound to prevent obesity could be developed (Higgins *et al.* 2020). Lorcaserin, a selective 5-HT$_{2C}$ agonist, was approved by the FDA in 2012 for the management of body weight. Lorcaserin's anorexigenic action is mediated by its ability to increase levels of proopiomelanocortin in the hypothalamus. Unfortunately, the efficacy of lorcaserin in promoting weight loss was modest. Moreover, due to an increased incidence of cancer in patients treated with lorcaserin, it was removed from the market in 2020.

5-HT_3 receptors are ligand-gated cation channels composed of five subunits that are expressed in a variety of brain regions but notably are present at high densities in the dorsal vagal complex of the brain stem (area postrema and nucleus tractus solitarius). This area is involved in the vomiting reflex, and 5-HT_3 antagonists (e.g., ondansetron, granisetron, palonosetron) are strong antiemetics and are frequently used to treat emesis experienced after surgery or related to cancer chemotherapy (Kovac 2016; Navari 2013). There are many potential 5-HT_3 receptor isoforms based on various combinations of the five subunits and through alternative mRNA splicing. Although there are currently no clinically available drugs that target the 5-HT_3 receptor for conditions other than emesis, ongoing preclinical studies are investigating the role of the 5-HT_3 receptor in anxiety, cognition, pain, and learning and memory (Fakhfouri *et al.* 2019). For example, in addition to its antidepressant activity, the SSRI vortioxetine may enhance cognition by antagonism of 5-HT_3 receptors (Riga *et al.* 2016).

Compared with the extensive work on 5-HT_1 and 5-HT_2 receptors, much less is known about the role of $5\text{-HT}_{4\text{-}7}$ receptors in neuropsychiatric disorders. The canonical signaling pathway for 5-HT_4, 5-HT_6, and 5-HT_7 receptors is through the G_s family of G proteins (stimulation of adenylyl cyclase activity), whereas the 5-HT_5 receptor couples predominantly to $G_{i/o}$ (inhibition of adenylyl cyclase) but can signal via a variety of different cascades (Noda *et al.* 2004). Preclinical studies suggest a role for 5-HT_4 receptors in cognition, mood (anxiety and depression), and feeding behavior (Bureau *et al.* 2010). Unfortunately, clinical studies have not been done, perhaps due to concerns about adverse effects associated with the cardiac and gastrointestinal actions of 5-HT_4 agonists (see Barnes *et al.* 2021). There are very few studies of behavioral effects mediated by 5-HT_5 receptors, perhaps due to the lack of selective ligands. Several studies have demonstrated a role for 5-HT_6 receptor antagonism in cognition, consistent with this receptor's localization in cortical neurons. These findings paved the way for clinical trials of 5-HT_6 antagonists, in conjunction with cholinesterase inhibitors, for treatment of Alzheimer's disease (Hung and Fu 2017). Although early findings appeared promising, subsequent studies failed to find a significant effect from two 5-HT_6 antagonists, idalopirdine and intepirdine, in improving cognition (Khoury *et al.* 2018). Paradoxically, it appears that 5-HT_6 agonists may have procognitive effects (Meneses *et al.* 2011). In preclinical studies, the 5-HT_7 receptor has been linked to circadian rhythm regulation, temperature, cognition, mood, pain, substance use disorders, and seizures (Blattner *et al.* 2019; Okubo *et al.* 2021). Although there are no selective 5-HT_7 ligands in clinical use, many drugs, including antidepressants and antipsychotics, have an affinity for 5-HT_7 receptors; however, the contribution of this receptor to these drugs' therapeutic efficacy or adverse-effect profile is not known. In 2018, a 5-HT_7 antagonist, JNJ-18038683, entered clinical testing for the treatment of cognitive impairment associated with bipolar disorder; as of June 2023, this trial is ongoing (ClinicalTrials.gov 2021).

Serotonin Transporters

The serotonin (5-HT) transporter (SERT [also called 5-HTT]) is the primary mechanism terminating serotonergic signaling. Located extrasynaptically on presynaptic serotonergic nerve terminals, SERT is responsible for high-affinity uptake of serotonin from extracellular fluid into the terminal, where serotonin is then either broken down enzymatically by MAO or repackaged into vesicles via the vesicular monoamine transporter 2 (VMAT2) (for a review, see German *et al.* 2015). SERT and other

biogenic amine transporters were originally thought to reside in the synaptic cleft, but electron microscopy studies have since revealed these transporters to reside extrasynaptically, predominantly on axons and axon terminals (e.g., Pickel and Chan 1999). The important implication from these findings is that serotonin neurotransmission can operate via paracrine (volume) transmission (see Fuxe *et al.* 2007; Borroto-Escuela *et al.* 2021). SERT is also found on nonserotonergic dendrites and glia, although it is more sparsely expressed on these cell types (Pickel and Chan 1999). SERT is found at its highest density in serotonin cell bodies in the dorsal and median raphe nuclei. It is broadly located in terminal regions, including limbic brain structures important in the regulation of mood and arousal states, such as hippocampus, amygdala, and entorhinal cortex (Hensler *et al.* 1994). First cloned in 1991 (Blakely *et al.* 1991; Hoffman *et al.* 1991), SERT is a member of the solute carrier 6 (SLC6) family and is encoded by the gene *SLC6A4*. It has 12 transmembrane-spanning domains, intracellular N-and C-termini, a large extracellular loop with glycosylation sites, and intra-and extracellular loops containing phosphorylation sites. (For comprehensive reviews of SERT structure, function, and regulation, see Kristensen *et al.* 2011, Pramod *et al.* 2013, and Ramamoorthy *et al.* 2011.)

SERT is a symporter (i.e., a membrane protein involved in the transport of two different molecules across the cell membrane in the same direction), deriving energy for transport of serotonin molecules through its co-transport with sodium ions into the nerve terminal. High sodium concentrations are maintained outside the neuron by the plasma membrane sodium/potassium ATPase pump. Serotonin, and other biogenic amines, use the electrochemical gradient created by high sodium levels outside the cell to gain entry. Thus, serotonin transport is not directly energy requiring. SERT itself is a dynamic protein. It can form oligomers (Jayaraman *et al.* 2021; Sitte *et al.* 2004) and is tightly regulated by many kinases, phosphatases, and auto-and heteroreceptors (Bermingham and Blakely 2016; Steiner *et al.* 2008). SERT is trafficked in and out of the plasma membrane and exists in both "on" and "off" states when in the plasma membrane. Psychostimulants and antidepressants that interact with SERT also regulate its trafficking and/or its activation state in a manner dependent on whether the drug is a transported substrate (e.g., MDMA) or a blocker (e.g., fluoxetine) (Ramamoorthy and Blakely 1999).

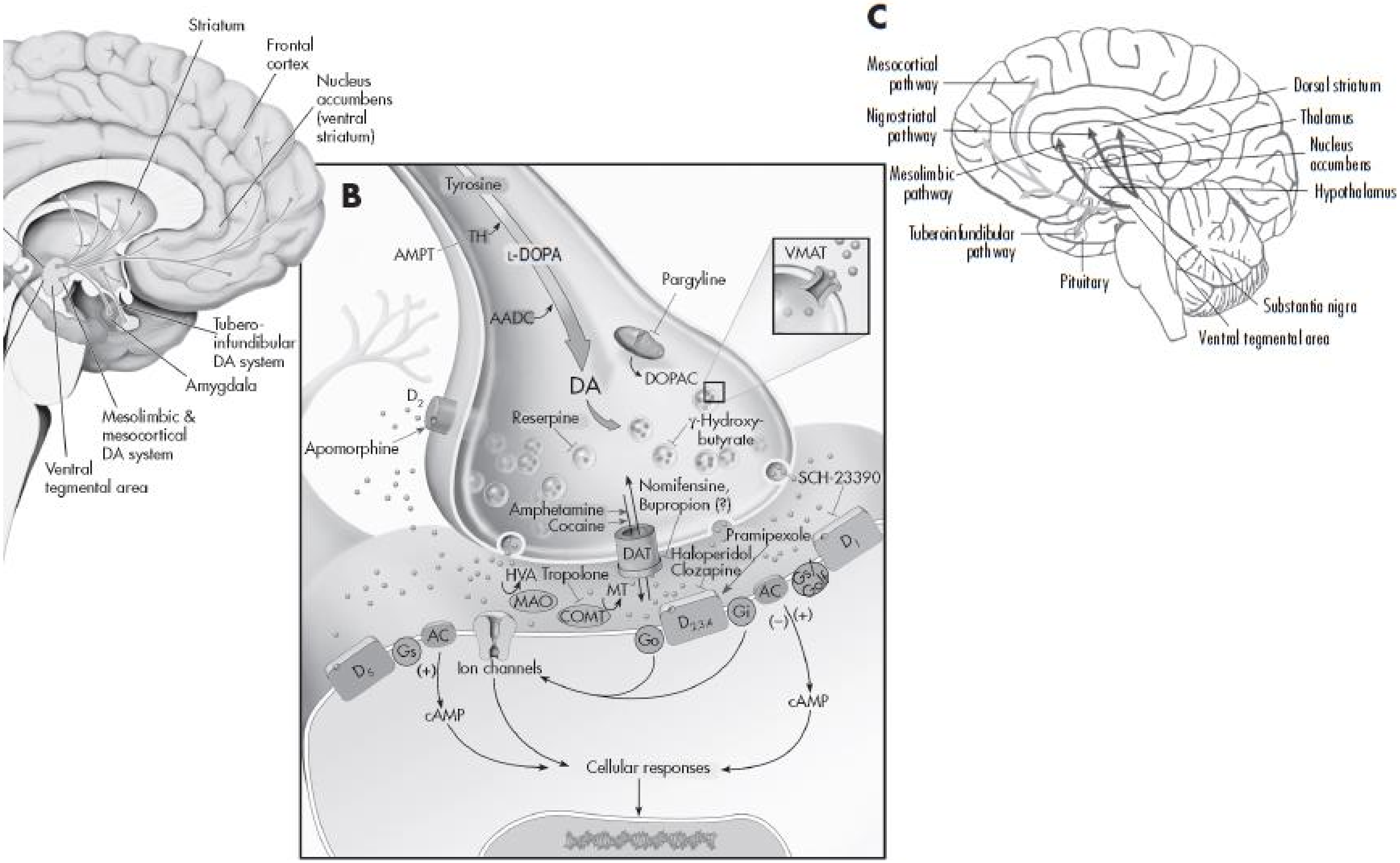
Dysfunction in serotonergic neurotransmission has long been linked to many psychiatric disorders, including depressive disorders, anxiety disorders, OCD, and autism spectrum disorder. Because serotonin is critical for normal brain development, abnormalities in serotonin neurotransmission during embryonic and postnatal development have been the focus of intense research. Genetic or pharmacological perturbations of SERT during development have been tied to autism spectrum disorder, as well as to increased anxiety and exaggerated stress response (Daws and Gould 2011). Not surprisingly, SERT, as a major regulator of the strength and duration of serotonin signaling, has been a primary target for development of therapeutics to treat these disorders. SSRIs, which act through blockade of SERT, are the most commonly prescribed pharmaceutical treatment for these psychiatric disorders, although evidence on their efficacy and tolerability is mixed (Cipriani *et al.* 2018). SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

In general, the majority of patients treated with SSRIs do not receive full symptom relief, bringing into question the therapeutic utility of increasing extracellular serotonin. However, it is now broadly accepted that transporters for biogenic amines are

promiscuous (i.e., capable of taking up biogenic amines other than their "native" neurotransmitter). For example, the norepinephrine and dopamine transporters (NET and DAT) are capable of serotonin uptake, and there is evidence that drugs that block SERT, NET, and DAT are therapeutically more efficacious than drugs that selectively block only one of these transporters (see Daws 2009; Sharma *et al.* 2015). In addition, there is rapidly growing evidence that organic cation transporters (OCTs) and the plasma membrane monoamine transporter (PMAT) play an important role in biogenic amine homeostasis in the brain (Daws 2021; Koepsell 2020). OCTs and PMAT have low affinity for serotonin transport but a high capacity to transport serotonin, meaning that when extracellular serotonin increases, as is expected following treatment with an SSRI, these so-called uptake-2 transporters for serotonin are able to efficiently clear serotonin from the extracellular fluid. In doing so, they effectively "keep a brake on" the ability of SSRIs to increase extracellular serotonin, which is thought to be required to trigger downstream events that lead to maximum therapeutic benefit. Because OCTs and PMAT are polyspecific organic cation transporters, their activity might also help account for poor treatment response to antidepressants that block NET (e.g., reboxetine) or DAT (e.g., bupropion) as well. The role of OCTs and PMAT in the treatment of psychiatric disorders is an area of active research.

Numerous gene variants of SERT have been identified (for reviews, see Kristensen *et al.* 2011 and Murphy and Lesch 2008). Among the most common gene variants is the serotonin transporter-linked polymorphic region (5-HTTLPR) polymorphism. Individuals who carry this variant have a variable number of tandem repeats (44 base pair insertion/deletion) in the SERT promotor region. Individuals who carry the short (s) variant have reduced expression of the SERT protein relative to individuals homozygous for the long (l) allele. Notably, the 5-HTTLPR polymorphism has been linked with numerous psychiatric disorders, including depression and anxiety-related disorders as well as alcohol use disorder (Caspi *et al.* 2003, 2010; Kristensen *et al.* 2011; Murphy and Lesch 2008). Worth noting is the finding that mouse models of this SERT gene variant, which have reduced SERT expression, have fivefold higher extracellular concentrations of serotonin than their wild-type counterparts (Mathews *et al.* 2004), bringing into question the dogma that low extracellular serotonin is linked to psychiatric disorders. Moreover, individuals carrying this polymorphism are reported to be less responsive to treatment with SSRIs (Serretti *et al.* 2007). In murine studies, the finding that a mouse model of this human gene variant displays increased expression of organic cation transporter type 3 (OCT3), presumably to compensate for the constitutive reduction in SERT (Baganz *et al.* 2008), raises the possibility that the activity of OCT3 may account for the poor therapeutic response to SSRIs in these individuals. It is known that long-term treatment with SSRIs downregulates SERT function and expression, and this downregulation is thought to contribute to the delay of weeks to months in the onset of therapeutic efficacy (e.g., Benmansour *et al.* 1999). Future studies examining potential compensation in "uptake-2" transporters may help provide mechanistic insights into why the benefits of SSRIs tend to wane after prolonged treatment in some individuals. Rare, nonsynonymous SERT gene variants have been linked to OCD and autism spectrum disorder. Notably, these SERT gene variants display a gain-of-function phenotype, which appears to be due to increased intrinsic SERT activity and/or increased expression in the plasma membrane (Veenstra-Vanderweele *et al.* 2012).

SERT is a prime regulator of serotonergic neurotransmission. What is clear from the literature is that genetic perturbations in SERT function that lead to either decreases or increases in extracellular serotonin are associated with a number of psychiatric disorders. SERT and its many regulators, as well as other transporters for serotonin, will continue to be a focus of research aimed at improving on current treatments for these disorders.


Striatum
Frontal cortex
Nucleus accumbens (ventral striatum)
Tubero-infundibular DA system
Amygdala
Mesolimbic & mesocortical DA system
Ventral tegmental area
B
Tyrosine
TH
AMPT
L-DOPA
AADC
DA
Pargyline
DOPAC
VMAT
D2
Apomorphine
Reserpine
γ-Hydroxy-butyrate
SCH-23390
Nomifensine, Bupropion (?)
Amphetamine
Cocaine
DAT
Pramipexole
Haloperidol, Clozapine
HVA
Tropolone
MAO
MT
COMT
D1
AC
Gs/Golf
Gi
Go
D2,3,4
(−)
(+)
D5
Gs
AC
(+)
Ion channels
cAMP
cAMP
Cellular responses
C
Mesocortical pathway
Nigrostriatal pathway
Mesolimbic pathway
Tuberoinfundibular pathway
Pituitary
Dorsal striatum
Thalamus
Nucleus accumbens
Hypothalamus
Substantia nigra
Ventral tegmental area

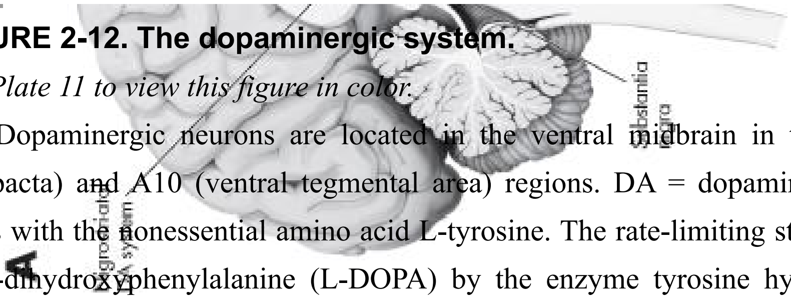


FIGURE 2-12. The dopaminergic system.

See Plate 11 to view this figure in color.

(A) Dopaminergic neurons are located in the ventral midbrain in the A9 (substantia nigra pars compacta) and A10 (ventral tegmental area) regions. DA = dopamine.**(B)** Synthesis of dopamine starts with the nonessential amino acid L-tyrosine. The rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase (TH). Aromatic L-amino acid decarboxylase (AADC) then converts L-DOPA to dopamine, which can be metabolized to 3,4-dihydroxyphenylacetic acid (DOPAC) by intraneuronal monoamine oxidase (MAO) or sequestered and stored in secretory vesicles by vesicular monoamine transporters (VMATs). Once released, dopamine acts on pre-and postsynaptic metabotropic receptors and is terminated via reuptake by perisomatic dopamine transporters (DATs). (Note that DATs are located extrasynaptically, not synaptically [as depicted in figure].) AMPT = a-methyl-*p*-tyrosine; cAMP = cyclic adenosine monophosphate; COMT = catechol-O-methyltransferase; HVA = homovanillic acid; MT = methoxytyramine. **(C)** Four separate dopamine pathways are present in the brain that play distinct roles in pathophysiology and therapeutic intervention: the mesocortical pathway (*yellow*), the nigrostriatal pathway (*blue*), the mesolimbic pathway (*red*), and the tuberoinfundibular pathway (*green*).

Source. **Figure parts A and B:** Reprinted from Figure 2-4 (pp. 66-67) in Drazinic CM, Szabo ST, Gould TD, Manji HK: "Neurotransmitters and Receptors in Psychiatric Disorders," in *The American Psychiatric Association Textbook of Psychopharmacology*, 5th Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Association Publishing, 2017, pp. 45-116. Copyright (c) 2017, American Psychiatric Association. Used with permission. **Figure part C:** Reprinted from Figure 1 (p. 3) of Yang S, Boudier-Reveret M, Choo YJ, Chang MC: "Association Between Chronic Pain and Alterations in the Mesolimbic Dopaminergic System." *Brain Sciences* 10(10):701, 2020 (https://doi.org/10.3390/brainsci10100701). Copyright (c) 2020 by the Authors. Licensee Multidisciplinary Digital Publishing Institute (MDPI), Basel, Switzerland. This article is an Open Access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

Dopaminergic System

An elegant biosynthetic pathway exists in the brain for catecholamine neurotransmitters. These neurotransmitters consist of a single amine group and a catechol nucleus (a benzene ring with two hydroxyl groups) (see Figure 2-1), and a single pathway is used in the generation of three distinct neurotransmitters: dopamine, norepinephrine, and epinephrine. This metabolic pathway (tyrosine - L-DOPA - dopamine - norepinephrine - epinephrine) is capable of generating one of these three neurotransmitters based solely on the enzymes expressed by a particular neuron. In the case of dopaminergic neurons, the enzymes tyrosine hydroxylase and aromatic L-amino acid decarboxylase (AADC; also known as DOPA decarboxylase) are highly expressed, whereas the enzymes responsible for subsequent metabolism of dopamine to norepinephrine are not present in appreciable quantities. This metabolic pathway is highly relevant for treatment of Parkinson's disease, a debilitating neurodegenerative disorder resulting in loss of dopamine neurons in the brain. Although there is no cure for this disease, a number of treatments are available that can control motor symptoms. These drugs typically mimic the effects of dopamine or increase the levels of dopamine in the brain. Interestingly, dopamine itself cannot be used to treat this disease because it is too polar to cross the blood-brain barrier and enter the CNS. Instead, the biological precursor for dopamine, L-dihydroxyphenylalanine (also known as levodopa or L-DOPA), is used because it can utilize an amino acid transporter system to enter the brain. L-DOPA is often administered in tandem with a peripherally acting AADC inhibitor to minimize peripheral side effects and to increase the amount of L-DOPA available to cross the blood-brain barrier. Since the 1970s, L-DOPA has been considered the gold standard for the treatment of Parkinson's disease; however, as the disease progresses, the side effects of L-DOPA increase. It is notable that the best available drug for the treatment of Parkinson's disease is one that was discovered more than 50 years ago.

The dopamine system in the brain can be divided into four distinct pathways--mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular--each with a unique function (Figure 2-12C) (Ungerstedt 1971). The *mesolimbic pathway* has cells located in the ventral tegmental area (VTA; A10 cell region) and projects to the ventral areas of the striatum, such as the nucleus accumbens. Dopamine release in the mesolimbic system is observed both with natural reinforcers (e.g., food, sex) and with most drugs of abuse. Dopamine transmission is thought to encode an error prediction signal wherein dopamine neurons fire when a reward is larger than predicted and show depressed activity when a reward is smaller than predicted (Schultz 1998). The *mesocortical pathway* also has its origin in the VTA and projects to the cerebral cortex, including limbic regions involved in cognition, such as the medial prefrontal cortex. The *nigrostriatal pathway* has cells located in the substantia nigra pars compacta (SNpc; A9 cell region) and provides dense innervation to the caudate and putamen,

where dopamine plays a significant role in movement. Indeed, the progressive and selective loss of dopamine neurons in the SNpc is a hallmark of Parkinson's disease. Finally, the *tuberoinfundibular pathway* consists of a population of dopamine neurons in the arcuate nucleus that inhibit prolactin release from the pituitary gland. The dopamine pathways are important from a therapeutic perspective; for example, blockade of the mesolimbic pathway is beneficial for the treatment of psychosis, but blockade of other dopamine pathways produces adverse effects (e.g., the EPS and hyperprolactinemia observed with some antipsychotic medications are due to blockade of the nigrostriatal and tuberoinfundibular pathways, respectively).

The activity of dopamine neurons can be regulated by both intrinsic properties and afferent pathways. Dopamine neurons exist in distinct states--an inactive state (hyperpolarized) and two active states (single spike and burst firing). On the basis of electrophysiological recordings in anesthetized rats, a model was proposed that differentiated tonic and phasic dopamine transmission (Grace 1991). This model posited that extrasynaptic dopamine levels are driven by the spontaneous (or tonic) firing of midbrain dopamine neurons, whereas synaptic dopamine levels are driven by periods of high-frequency activity, known as burst firing. The phasic burst firing of dopamine neurons and the accompanying release of synaptic dopamine normally occur in response to primary rewards (until they become fully predicted) and reward-predicting stimuli (Schultz 1998). A third dopamine neuron activity state--population activity--was demonstrated on the basis of the observation that a number of dopamine neurons (estimated at 50%) are not spontaneously active in vivo (Grace *et al.* 2007). The role of these silent dopamine neurons appears critical, given that they provide a gain of function to the dopamine signal. Through regulation of the number of spontaneously

active dopamine neurons, the magnitude of the dopamine signal (both tonic and phasic) can be manipulated. Aberrant regulation of this important gain of function is thought to contribute to the positive symptoms (i.e, paranoia, hallucinations, delusions) of schizophrenia (Grace *et al.* 2007).

Dopaminergic Receptors

Following early debates over the existence of multiple subtypes of dopamine receptors in the 1970s, classical pharmacological techniques provided evidence of the existence of two subtypes of dopamine receptors, D_1 and D_2 (Stoof and Kebabian 1984). It was subsequently determined that these two receptor subtypes each represent multiple receptors with similar characteristics. These receptors have been classified as D_1-like and D_2-like and consist of five identified dopamine receptors (D_1, D_2, D_3, D_4, and D_5), with D_1 and D_5 receptors being considered D_1-like and D_2, D_3, and D_4 receptors considered D_2-like. D_1-like receptors couple to stimulatory G proteins (G_s), which activate adenylyl cyclase, leading to production of the second messenger cAMP. In contrast, D_2-like receptors couple to inhibitory G proteins (G_i), which inhibit adenylyl cyclase and activate K^+ channels, resulting in membrane hyperpolarization. While it is often thought (and taught) that GPCRs exist and act as monomers, current evidence suggests that these receptors are capable of forming pharmacologically active homo- and heterodimers. Interestingly, dopamine receptors can form distinct heterodimer receptors, composed of both D_1-like and D_2-like subunits. These heterodimer receptors require binding of an agonist to both orthosteric binding sites for receptor activation. Moreover, whereas monomeric D_1-like and D_2-like receptors couple to G_s and G_i, respectively, D_1-D_2 receptor complexes are thought to signal predominantly through

$G_{q/11}$ protein and the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) second-messenger system (Rashid *et al.* 2007). The discovery of heterodimer receptors not only provides a unique signaling mechanism for dopamine but also may have ramifications for pharmacotherapies targeting dopamine system function, such as the antipsychotic drugs. The D_1-like and D_2-like receptor classes also differ in their affinity for dopamine; D_2-like receptors have a significantly greater affinity for dopamine than do D_1-like receptors. This difference in receptor affinity suggests that dopamine signaling may depend on the type of dopamine neuron activity, with D_1 receptors primarily activated during periods of dopamine neuron burst firing and D_2-like receptors primarily activated by tonic dopamine. Thus, D_2-like receptors can respond to a broader range of stimuli.

Within the CNS, D_1-like and D_2-like receptors are largely concentrated in striatal regions (i.e., caudate, putamen, and nucleus accumbens), where they differentially regulate motor function. In addition, D_1-like receptors are present in limbic regions, including the amygdala and frontal cortex.

D_1-like receptors (D_1 and D_5). The D_1-like subgroup consists of D_1 and D_5 receptors. These two receptor types have similar pharmacological profiles and have been shown to couple to G_s or G_{olf} (a G protein originally thought to be present exclusively in olfactory tissue but now known to be present in limbic areas as well), resulting in activation of adenylyl cyclase and increases in intracellular cAMP. Thus, in general, the D_1-like receptors are excitatory, increasing the likelihood of firing of D_1-expressing medium spiny neurons. Receptors of the D_1-like family are intron-less in their respective coding regions. The presence of introns in a gene can lead to alternatively spliced transcripts where the exons are joined in different combinations. Thus, there

are no known alternative transcripts (c.f. the D_2-like receptors where alternative splicing directs the expression of multiple isoforms). D_1-like receptors are highly expressed in caudate and putamen, where they are localized to medium spiny neurons of the "direct pathway," which sends direct inhibitory projections to the ventral mesencephalon (substantia nigra pars reticulata [SNpr]/internal globus pallidus [GPi]). As described above (see "Dopaminergic System"), degeneration of dopamine neurons in the nigrostriatal pathway is a key pathology in Parkinson's disease, and L-DOPA has been the mainstay of treatment for Parkinson's disease for more than 50 years. Robust evidence from both preclinical and clinical studies suggests that targeted activation of dopamine D_1 receptors may be effective in treating Parkinson's disease as well as in ameliorating the side effects of L-DOPA therapy (Hall *et al.* 2019). Furthermore, given that L-DOPA depends on AADC for conversion to dopamine, the efficacy of L-DOPA decreases in late-stage Parkinson's disease, when loss of dopamine neurons results in loss of AADC. Several single-dose clinical studies of D_1 agonists have demonstrated strong antiparkinsonian effects on motor symptoms, and primate studies suggest that selective D_1 agonists may provide profound symptomatic relief even when the degree of nigrostriatal degeneration is so severe that current drugs are ineffective (Mailman *et al.* 2021). Unfortunately, early D_1 receptor agonists had pharmacological limitations and dose-limiting side effects (particularly hypotension and tachycardia) that precluded their clinical use. However, more recently developed compounds, such as the orally active selective D_1/D_5 partial agonist PF-06412562, display potential antiparkinsonian efficacy without producing overt changes in cardiovascular function (Huang *et al.* 2020; Papapetropoulos *et al.* 2018).

D_1 receptors. D_1 receptors are the predominant dopamine receptor in the frontal cortex, where they play a central role in higher-order functions such as working memory and cognitive flexibility (Goldman-Rakic 1995). Moreover, dopamine D_1 receptor expression or signaling is thought to be compromised in a variety of psychiatric disorders, including schizophrenia. Considerable research has been focused on developing D_1 agonists for the treatment of cognitive deficits in schizophrenia, given that these symptoms are not well treated by conventional antipsychotics. Overall, although increased signaling at dopamine D_1 receptors may improve cognitive function in schizophrenia, it is important to note that prefrontal dopamine transmission operates within a defined working range for effective cortical function, in which both increases and decreases can induce cognitive deficits. Despite the importance of the D_1 receptor as a therapeutic target, there has been a notable lack of clinically effective agents. The orally active selective D_1/D_5 partial agonist PF-06412562 (discussed earlier in the context of treatment for Parkinson's disease) demonstrates procognitive effects in preclinical models and is currently being evaluated for safety and efficacy in schizophrenia patients (Abi-Dargham *et al.* 2022).

D_5 receptors. The dopamine D_5 receptor was cloned in the early 1990s. This receptor, which shares about 80% homology with the D_1 receptor, also possesses signal transduction and pharmacology similar to those of the D_1 receptor; however, the D_5 receptor is reported to have a 10-fold higher affinity for the endogenous agonist dopamine. The D_5 receptor is neuron-specific and is located primarily in limbic areas of the brain. At present, there are no compounds that pharmacologically differentiate it from the D_1 receptor (Arnsten *et al.* 2017).

D_2-like receptors (D_2, D_3, and D_4). The D_2-like subgroup consists of D_2, D_3, and D_4 receptors. These three receptor types have similar pharmacological profiles and are largely coupled to G_i/G_o proteins.

D_2 receptors. D_2-like receptors are found on indirect pathway neurons that are indirectly connected to the GPi/SNpr through the globus pallidus pars externa (GPe) and the subthalamic nucleus (STN). Dopamine D_2-like receptors are found not only on postsynaptic targets but also on dopamine neurons themselves, both at the cell body and at the presynaptic nerve terminal. D_2-like receptors on dopamine neurons function as autoreceptors, and activation of the receptor can decrease neurotransmitter release and inhibit neuronal activity through well-known interactions with voltage-gated Ca^{2+} channels and GIRK channels. Because they contain introns within their coding regions, D_2-like receptors are structurally more complex than D_1-like receptors (i.e., the D_2 receptor contains six introns, the D_3

receptor five, and the D_4 receptor three). These introns give rise to distinct isoforms due to alternative mRNA splicing. Indeed, one important mechanism for modulating D_2 signaling is alternative splicing of an 87-base-pair exon between introns 4 and 5, resulting in long (D_{2L}) and short (D_{2S}) isoforms. Functionally distinct roles for D_{2S} and D_{2L} receptors have been proposed, based largely on characterization of mice lacking these isoforms. Such studies have suggested that the long isoform of the dopamine D_2 receptor is primarily located on postsynaptic medium spiny neurons in striatum and basal forebrain. In contrast, the short isoform is thought to contribute to the presynaptic regulation of dopamine release (De Mei *et al.* 2009). However, the individual contributions of the two isoforms to physiological and pathophysiological processes remain unclear. These isoforms differ in the third cytoplasmic loop, which plays a significant role in coupling the receptor to various intracellular partners. Thus, while both receptor isoforms signal through G_i proteins, differences in the downstream signaling of the two isoforms have been demonstrated. At present, there are no pharmacological tools that can differentiate the short and long forms of the two isoforms.

As discussed extensively elsewhere in this textbook (see Chapter 25, "Classic Antipsychotic Medications"), D_2 receptors have long been a focus in the treatment of psychosis. A significant literature from both human imaging and preclinical research has demonstrated that psychosis is associated with an increase in presynaptic dopamine bioavailability in the striatum (Howes *et al.* 2012). This increase in dopamine bioavailability is likely attributable to aberrant regulation of dopamine neuron activity in the VTA. This hypothesis is supported by the clinical efficacy of both first-and second-generation antipsychotics, which are largely defined by their high-affinity antagonism of the D_2 receptor. The second-generation (or atypical) antipsychotics are less likely to produce EPS, a characteristic thought to be associated with these agents' reduced affinity for the D_2 receptor with additional blockade of 5-HT_{2A} receptors.

D_3 receptors. In the 1990s, molecular cloning led to expansion of the dopamine receptor family beyond the existing D_1 and D_2

receptors. D_3 receptors have a more limited anatomical distribution than D_2 receptors, which makes them a potential novel target for development of drugs devoid of the EPS classically elicited by D_2 antagonists. Specifically, D_3 receptors are predominantly located in limbic areas, such as ventral striatum, thalamus, hippocampus, and cortex, and have a higher affinity for dopamine than do D_2 receptors. Furthermore, in contrast to both D_1 and D_2 receptors,

which are located either in perisynaptic sites or on dendrites and dendritic spines of medium spiny neurons, D_3 receptors appear to be localized to glutamatergic synapses (Sokoloff *et al.* 2013). Given their high affinity for dopamine and localization away from release sites, D_3 receptors appear to be well suited for detecting tonic, extrasynaptic dopamine transmission. Numerous studies have investigated the association between the dopamine D_3 receptor and schizophrenia. The D_3 receptor gene (*DRD3*) contains a polymorphism resulting in a serine-glycine substitution in the N-terminus of the receptor. Furthermore, a significant association has been demonstrated between the *DRD3* polymorphism and schizophrenia, with a meta-analysis of previous studies demonstrating significant associations (Dubertret *et al.* 1998). Thus, D_3 dopamine receptors are attractive targets for therapeutic intervention in schizophrenia due to their influence on dopamine system function and potentially positive effects on cognition. Indeed, results obtained from studies examining D_3 receptor antagonists indicate that blockade of D_3 receptors produces antipsychotic-like effects in rodent models used to evaluate both positive and negative symptoms (Maramai *et al.* 2016). Current clinical data from studies examining the efficacy of D_3 receptor antagonists/partial agonists in schizophrenia are inconclusive (Kiss *et al.* 2021), and additional studies are needed to separate the relative antipsychotic effects of D_2 and D_3 receptors.

D_4 receptors. The D_4 receptor has received much interest in psychopharmacological research because of the finding that clozapine has a high affinity for this receptor. Clozapine is the prototypical atypical antipsychotic, reported to be significantly more effective than 14 other antipsychotic drugs in a meta-analysis (Leucht *et al.* 2013). Clozapine's success led to the development of other selective D_4 (and D_4/5-HT_{2A}) receptor antagonists without EPS-inducing effects for use in the treatment of schizophrenia. Just 6 years after the discovery of the D_4 receptor, Merck published a series of manuscripts describing preclinical and clinical efficacy studies of L-745,870, a selective, CNS-penetrant, D_4-preferring antagonist (Bristow *et al.* 1997). Unfortunately, a third of the patients in this clinical trial discontinued the study due to a lack of therapeutic response, and the placebo group outperformed the D_4 antagonist group, with a subset of patients reporting worsening of symptoms. Similar disappointing results were observed in clinical studies of sonepiprazole, a highly selective D_4 receptor antagonist, which showed no benefits in schizophrenia patients (Corrigan *et al.* 2004). These findings dampened enthusiasm for the D_4 receptor as a therapeutic target for schizophrenia. Regrettably, the lack of clinical efficacy shown by these agents in CNS trials is a relatively common finding, with more than 90% of trials failing due to a lack of efficacy (sometimes associated with a high placebo response rate) (Gribkoff and Kaczmarek 2017). Indeed, failure rates are highest for drugs with a new mechanism of action (e.g., D_4 ligands) and for diseases whose etiology and pathogenesis have not been conclusively elucidated (e.g., schizophrenia). Nonetheless, research examining the potential utility of D_4 receptor ligands in other disorders, such as substance use disorders and L-DOPA-induced dyskinesia, is ongoing. This research is based on expression of the D_4 receptor in the human brain, which is predominantly localized to the cerebral cortex (including frontal cortex), hippocampus, and dorsal-medial thalamus. It should be noted that similar to the D_2 receptor gene, the D_4 receptor gene is highly polymorphic, with a variable number of tandem repeats of 48 nucleotides, ranging from 2 to 11 isoforms (D4.2-D4.11). The role of these isoforms in the pathophysiology of mental health disorders remains to be elucidated.

Dopamine Transporters

The primary mechanism for terminating the effects of dopamine signaling is uptake via the high-affinity DAT into the presynaptic terminal, where dopamine is either broken down enzymatically or repacked into vesicles via VMATs (German *et al.* 2015). Like SERT, DAT is a membrane-spanning protein. First cloned in 1991 (Giros *et al.* 1991; Kilty *et al.* 1991; Shimada *et al.* 1991), DAT is encoded by the gene *SLC6A3* (solute carrier family 6, member 3) and is located perisynaptically on dopamine nerve terminals as well as on somatodendritic sites within the VTA and the SNpc. Unlike SERT, DAT is present at its highest density in terminal field regions, including striatum, nucleus accumbens, and olfactory tubercle, and at its lowest density in cell body regions, including the VTA and the SNpc. Given the extrasynaptic location of DAT, dopamine neurotransmission also occurs in the form of paracrine signaling (Rice and Cragg 2008). As is the case for other monoamine transporters, DAT functions as a symporter, moving dopamine across the membrane using the concentration gradient of Na^+ (generated by the plasma membrane Na^+/K^+ ATPase) as the driving force. Like other neurotransmitter transporters, DAT can form oligomers (Jayaraman *et al.* 2021; Sorkina *et al.* 2021) and is tightly regulated by a complex array of signaling pathways (for comprehensive reviews of DAT structure, function, and regulation, see German *et al.* 2015; Kristensen *et al.* 2011; Pramod *et al.* 2013; Ramamoorthy *et al.* 2011; Ryan *et al.* 2021).

It is important to note that whereas the DAT is the primary mechanism terminating dopamine signaling, other transporters are able to transport dopamine across the membrane. For example, the PMAT and OCTs are nonselective cation transporters with relatively low affinity for monoamines but a high capacity to transport them. As discussed in the section on SERTs (see "Serotonin Transporters"), these transporters are being examined as potential targets for the development of novel antidepressant drugs (Daws 2009, 2021) as well as of treatments for psychostimulant use disorder (Maier *et al.* 2021). In the medial frontal cortex, dopamine is taken up predominantly by the NET, a circumstance that goes against the former dogma that transporters selectively move only their respective neurotransmitter (Moron *et al.* 2002). More importantly, this transporter promiscuity has potential therapeutic relevance in that norepinephrine reuptake inhibitors (e.g., the antidepressants desipramine and venlafaxine) may lead to increases in dopamine levels within the prefrontal cortex (Tanda *et al.* 1994). Indeed, a role for dopamine in depression is supported by the effectiveness of the atypical antidepressant bupropion, which is chemically unrelated to other classes of antidepressant agents. Bupropion is a relatively weak dopamine and norepinephrine reuptake inhibitor, with efficacy comparable to that of other antidepressants. DAT is also a primary target for psychomotor stimulants, where drugs such as amphetamine and cocaine act to inhibit DAT function, resulting in increases in extracellular dopamine. A large, rapid increase in dopamine signaling is thought to underlie the euphoria (or "high") associated with stimulant drugs when they are administered via inhalation or nasal insufflation.

The increasing availability of whole-genome sequencing has led to the observation that genetic polymorphisms in the DAT gene (which influence the expression and/or

function of the transporter) are associated with neuropsychiatric disorders such as attention-deficit hyperactivity disorder (ADHD), Parkinson's disease, schizophrenia, and substance use disorders (German *et al.* 2015; Gowrishankar *et al.* 2014). The DAT is also a pharmacological target, particularly for treatment of ADHD, one of the most common neurobehavioral disorders in children, which affects academic achievement and social interactions. When administered at low dosages in a sustained-release formulation, stimulant medications (e.g., amphetamine and methylphenidate) can effectively treat symptoms of ADHD, with an effect size comparable to, if not better than, those of most other psychiatric medications (Leucht *et al.* 2012). In children with ADHD, DAT inhibitors have been demonstrated to increase dopamine levels, resulting in improvements in attention and task-oriented behavior (Drechsler *et al.* 2020).

DAT is a key regulator of dopaminergic neurotransmission. Gene variants in DAT expression and/or function that cause perturbed dopamine signaling are associated with a number of psychiatric and motor disorders, as well as with substance use disorders. DAT and its many regulators, as well as other transporters for dopamine, are the focus of continued research efforts to better understand the etiology of these disorders and their treatment.

Noradrenergic System

Norepinephrine, also known as noradrenaline, is a neurotransmitter present in the CNS and the peripheral sympathetic nervous system that plays an essential role in the regulation of arousal, attention, cognitive function, and response to stress. Norepinephrine (see Figure 2-1) is a monoamine synthesized from the amino acid L-tyrosine within neurons that express the enzymes tyrosine hydroxylase and dopamine b-hydroxylase; briefly, dietary L-tyrosine permeates the blood-brain barrier and is transported to neuronal presynaptic terminals, where it is converted to L-DOPA by tyrosine hydroxylase (i.e., the rate-limiting step). L-DOPA is then decarboxylated by AADC to produce dopamine. Finally, in neurons that contain the enzyme dopamine b-hydroxylase, dopamine is converted to norepinephrine; cells that contain the enzyme phenylethanolamine-*N*-methyl transferase are also able to convert norepinephrine to epinephrine (Figure 2-13).

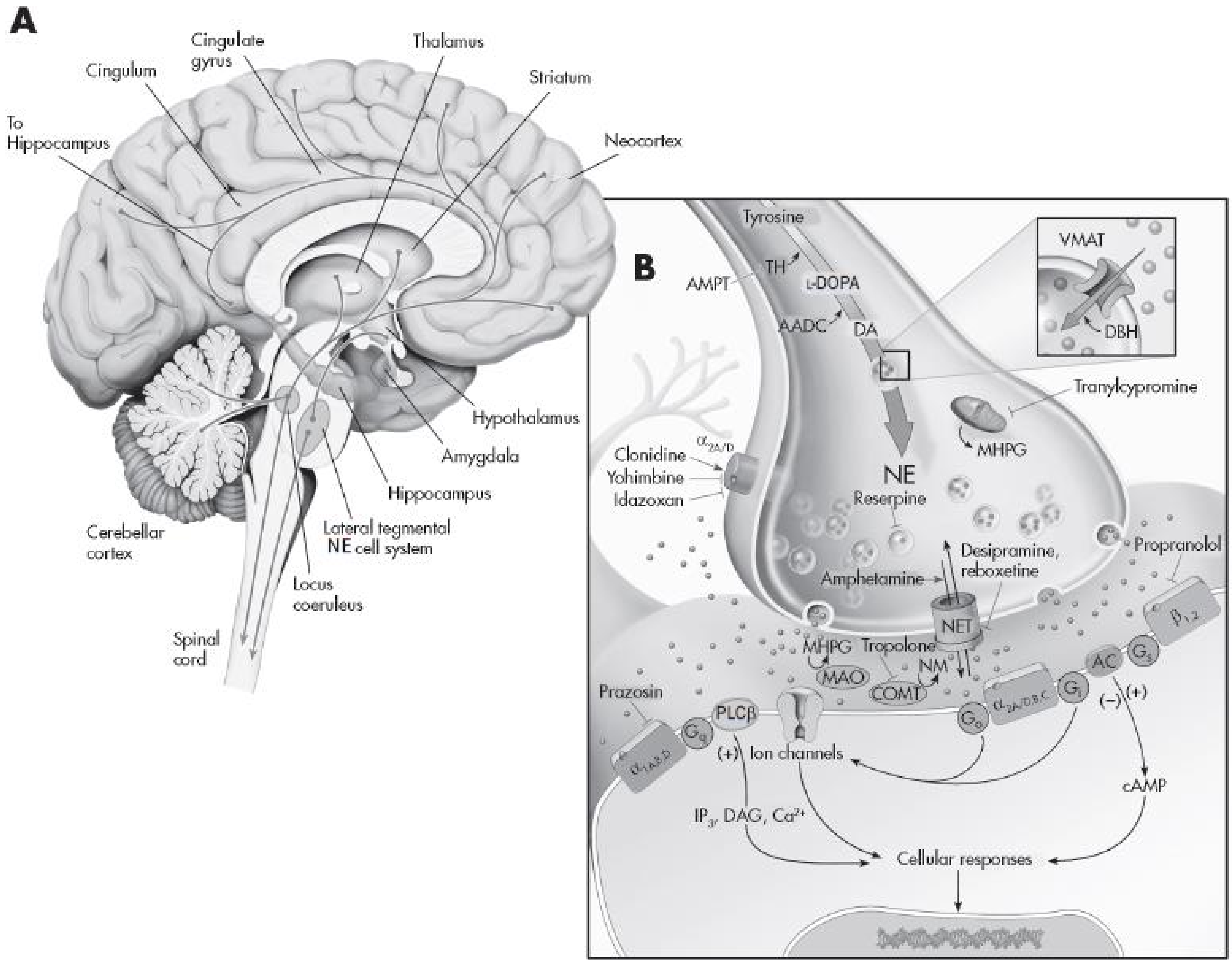

A
Cingulate gyrus
Thalamus
Cingulum
Striatum
To Hippocampus
Neocortex
Hypothalamus
Amygdala
Hippocampus
Cerebellar cortex
Lateral tegmental NE cell system
Locus coeruleus
Spinal cord
B
Tyrosine
TH
AMPT
L-DOPA
AADC
DA
VMAT
DBH
Tranylcypromine
MHPG
NE
Reserpine
α2A/D
Clonidine
Yohimbine
Idazoxan
Desipramine, reboxetine
Amphetamine
Propranolol
NET
β1,2
MHPG
Tropolone
NM
MAO
COMT
AC
Gs
Gi
α2A/D,B,C
Go
(−)
(+)
Prazosin
PLCβ
Gq
α1A,B,D
(+)
Ion channels
cAMP
IP3, DAG, Ca2+
Cellular responses

FIGURE 2-13. The noradrenergic system *(opposite page)*.

See Plate 12 to view this figure in color.

(A) Noradrenergic neurons of the locus coeruleus are located in the pons of the brain stem. **(B)** Synthesis of norepinephrine (NE) starts with the amino acid L-tyrosine, which is actively transported into presynaptic NE nerve terminals from extracellular fluid. The rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase (TH). Aromatic L-amino acid decarboxylase (AADC) converts L-DOPA to dopamine. Dopamine is then packaged into vesicles, by vesicular monoamine transporters (VMATs), and hydroxylated by dopamine b-hydroxylase (DBH) in the presence of O_2 and ascorbate to form NE. Once released from the presynaptic terminal, NE can interact with a variety of presynaptic and postsynaptic receptors. Presynaptic regulation of NE neuron firing activity and release occurs through somatodendritic (not shown) and nerve terminal a_2 adrenoreceptors, respectively. Binding of NE to G proteins (G_o, G_i, etc.) that are coupled to adenylyl cyclase (AC) and phospholipase C beta (PLCb) produces a cascade of second-messenger and cellular effects. NE's action is terminated when it is taken back into the presynaptic neuron via NE transporters (NETs). (Note that NETs are located extrasynaptically, not synaptically [as depicted in figure].) Once inside the neuron, NE can either be repackaged into vesicles for reuse or undergo enzymatic degradation. AMPT = a-methyl-*p*-tyrosine; cAMP = cyclic adenosine monophosphate; COMT = catechol-O-methyltransferase; DA = dopamine; DAG = diacylglycerol; IP_3 = inositol 1,4,5-triphosphate; MAO = monoamine oxidase; MHPG = 3-methoxy-4-hydroxyphenylglycol; NM = normetanephrine.

Source. Reprinted from Figure 2-5 (pp. 74-75) in Drazinic CM, Szabo ST, Gould TD, Manji HK: "Neurotransmitters and Receptors in Psychiatric Disorders," in *The American Psychiatric Association Textbook of Psychopharmacology*, 5th Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Association Publishing, 2017, pp. 45-116. Copyright (c) 2017, American Psychiatric Association. Used with permission.

Norepinephrine in the CNS controls arousal and alertness and influences cognitive functions such as working memory, fear memory retrieval, attention, and spatial learning. In addition to these actions in the CNS, norepinephrine and epinephrine released in the periphery by the sympathetic nervous system and neuroendocrine chromaffin cells in the adrenal medulla are crucial in preparing the body for the "fight or flight" stress response through modulation of several physiological outputs, such as cardiovascular function, gastrointestinal motility and secretion, bronchiole dilation, and glucose metabolism.

Within the CNS, the main clustering of norepinephrine-producing neurons lies in the locus coeruleus (Latin meaning "blue spot"--named for its bluish appearance in nonstained brain tissue, due to the presence of melanin granules in these neurons) (Schwarz and Luo 2015). The locus coeruleus, located in the pons, is responsible for approximately 90% of norepinephrine innervation of forebrain and produces more than 70% of all norepinephrine in the brain (see Figure 2-13). The widespread efferent innervation of the locus coeruleus suggests that the noradrenergic system, rather than having a specific role in sensory or motor outputs, plays a modulatory and integrative

role by regulating the "signal-to-noise ratio" of other neuronal systems, either excitatory or inhibitory. The net result is an enhancement of synaptic transmission in the target circuits that regulate wakefulness and arousal and facilitate sensory signal detection; indeed, increased activity in locus coeruleus neurons and increased norepinephrine release are observed especially in response to physiological or environmental challenges and stressful stimuli (Jacobs *et al.* 1991; Morilak *et al.* 2005). For this reason, modulation of the noradrenergic system has classically been considered central to stress responsivity. However, it is also clear that the noradrenergic network has a role in regulation of a wide range of core cognitive functions, including attention, working memory, and behavioral flexibility (Sara 2009; Valentino and Van Bockstaele 2008).

The locus coeruleus was originally considered to be a homogeneous group of neurons, but technological advances in neuronal tracing, optogenetics, chemogenetics, electrophysiology, and genetic fate mapping have revealed that the locus coeruleus is likely divided into distinct subgroups of cells that receive selective inputs from other brain regions and have relatively circumscribed projection targets in the forebrain. Notably, locus coeruleus neurons that project to functionally related forebrain regions tend to display synchronous firing activity (Chandler *et al.* 2019; Totah *et al.* 2019). The various subpopulations of locus coeruleus neurons also appear to express developmentally distinct genetic markers. Thus, the specificity of noradrenergic signaling in the brain may result not only from specific adrenergic receptors present on postsynaptic elements of target cells but also from diverse ensembles of locus coeruleus neurons and their specific integration within different functional networks (Poe *et al.* 2020).

Dysregulation of the noradrenergic system alters the response to stress, can increase anxiety, and produces cognitive and behavioral deficits associated with a number of psychopathologies, including Alzheimer's and Parkinson's diseases, ADHD, and schizophrenia (Borodovitsyna *et al.* 2017). It is therefore not surprising that modulation of locus coeruleus activity is important for maintaining effective cognitive function and stress responsivity. The pro-stress neuropeptide corticotropin-releasing factor (CRF) is a key regulator of the locus coeruleus-norepinephrine system. Preclinical studies have found that acute release of CRF from amygdala terminals projecting to the locus coeruleus that occurs after an acute stress exposure increases locus coeruleus neuron firing and promotes an adaptive response by increasing vigilance and behavioral flexibility. Conversely, chronic CRF release and tonic stimulation of locus coeruleus-norepinephrine neurons increase anxiety and depressive-like behaviors (McCall *et al.* 2015; Valentino and Van Bockstaele 2008). Moreover, studies have found that in comparison with males, females show increased sensitivity of locus coeruleus neurons to the effects of CRF, which may help to explain the increased incidence of posttraumatic stress disorder (PTSD) and depressive disorders in human females (Bangasser *et al.* 2016). Another regulator of the noradrenergic system that has attracted attention recently is the endocannabinoid system, which acts as an antistress modulator, potentially by decreasing release of CRF in locus coeruleus afferents (Wyrofsky *et al.* 2019). Finally, it is notable that the locus coeruleus itself also releases neuropeptides such as galanin, neuropeptide Y, cocaine-and amphetamine-regulated transcript, and BDNF; additionally, locus coeruleus-norepinephrine neurons can release dopamine (Beas *et al.* 2018).

Norepinephrine Receptors

Norepinephrine's actions are mediated by a-adrenergic receptors (a_1-ARs and a_2-ARs) and b-adrenergic receptors (b_1-ARs, b_2-ARs, and b_3-ARs), all of which are GPCRs (Table 2-3). In general, a_1-ARs and b-ARs enhance neurotransmission and plasticity, promoting stimulatory effects in the CNS, whereas a_2-ARs have inhibitory effects, such as reducing norepinephrine release and decreasing neuronal excitability. Nonselective agonists bind to ARs with different affinities, and include norepinephrine and dopamine (both of which bind to a_1, a_2, and b_1 ARs) as well as epinephrine (which binds to all classes of ARs).

TABLE 2-3. Major noradrenergic receptor subtypes

Receptor type	Subtype	Action	G-coupled mechanism
a_1	a_{1A}, a_{1B}, a_{1D}	Smooth muscle, mucosa, and gastrointestinal contraction; vasoconstriction and mydriasis. Activation produces anorexia, decreased excitability in the temporal cortex, and decreased excitatory postsynaptic potentials.	G_q; phospholipase C (PLC) activation, inositol 1,4,5-trisphosphate (IP_3), diacylglycerol, increase in calcium

Note. cAMP = cyclic adenosine monophosphate.

Source. Adapted from Table 1 (p. 1626) in Haass-Koffler CL, Swift RM, Leggio L: "Noradrenergic Targets for the Treatment of Alcohol Use Disorder." *Psychopharmacology (Berlin)* 235:1625-1634, 2018 (https://doi.org/10.1007/s00213-018-4843-6). Copyright (c) 2018. This is a U.S. Government work and not under copyright protection in the U.S.; foreign copyright protection may apply.

Receptor type	**Subtype**	**Action**	**G-coupled mechanism**
a_2	a_{2A}, a_{2B}, a_{2C}	Smooth muscle contraction/relaxation, norepinephrine inhibition, platelet activation, inhibition of insulin release, negative feedback in neuronal synapses, presynaptic inhibition of norepinephrine release in the CNS	G_i; adenylate cyclase inactivation (cAMP) decrease
b_1	--	Increased cardiac output; increased amylase secretion, renin secretion from kidney, and ghrelin from stomach	G_s; adenylate cyclase activation (cAMP) increase
b_2	--	Smooth muscle relaxation, glycogenolysis and gluconeogenesis, stimulation of insulin secretion, increased renin secretion. In the brain, b_2 receptors are involved in immune communication and flight-or-fight response.	G_s (but also G_i); adenylate cyclase inactivation (cAMP) increase
b_3	--	Enhanced lipolysis, promotion of bladder relaxation. Some b_3 agonists have antistress properties in animal models.	G_s; adenylate cyclase activation (cAMP) increase

Note. cAMP = cyclic adenosine monophosphate.
Source. Adapted from Table 1 (p. 1626) in Haass-Koffler CL, Swift RM, Leggio L: "Noradrenergic Targets for the Treatment of Alcohol Use Disorder." *Psychopharmacology (Berlin)* 235:1625-1634, 2018 (https://doi.org/10.1007/s00213-018-4843-6). Copyright (c) 2018. This is a U.S. Government work and not under copyright protection in the U.S.; foreign copyright protection may apply.

Alpha$_1$ receptors further subdivide into a_{1A}, a_{1B}, and a_{1D} adrenergic receptors. These receptors are located postsynaptically in brain regions including the locus coeruleus, olfactory bulb, cerebral cortex, dentate gyrus, amygdala, and thalamus. a_1-ARs have intermediate binding affinity to norepinephrine and couple to Ga_q proteins that activate PLC. PLC converts phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol on the cell membrane. IP_3 is released to the cytosol and binds to transmembrane IP_3 receptors located on the endoplasmic reticulum, which functions as a channel to release calcium from the endoplasmic reticulum to the cytosol. Diacylglycerol remains in the cell membrane and activates PKC, which phosphorylates other proteins. These combined effects produce excitatory cellular effects. Prazosin is an antagonist of a_1-ARs that has been approved for treatment of hypertension and has shown promising effects in treatment of PTSD-associated nightmares (Akinsanya *et al.* 2017). Additionally, in preclinical studies, a_1-AR antagonists (i.e., prazosin, terazosin, and WB-4101) decreased stimulant drug-induced locomotor hyperactivity (a predictor of drug abuse liability) (Schmidt and Weinshenker 2014). Human studies have shown that prazosin and doxazosin (another a_1-AR antagonist) can be effective as potential treatments for alcohol use disorder (Farokhnia *et al.* 2019).

Alpha$_2$ receptors--subdivided into a_{2A}, a_{2B}, and a_{2C} adrenergic receptors--have the highest binding affinity for norepinephrine among the different subtypes of noradrenergic receptors. Alpha$_2$ receptors are located both presynaptically and postsynaptically in brain regions including the locus coeruleus, amygdala, and hypothalamus. These receptors couple to the $Ga_{i/o}$ proteins, which inhibit adenylate cyclase and lower the production of cAMP, producing inhibitory cellular effects. In noradrenergic neurons, a_2 receptors act as autoreceptors (i.e., norepinephrine binding to a_2-ARs in presynaptic noradrenergic terminals prevents further release of norepinephrine). Therefore, activation of these receptors lowers noradrenergic signaling. Other agonists of a_2-ARs include methyldopa, guanfacine, and clonidine. In line with the general idea that a_2-ARs act in opposition to a_1-ARs, activation of a_2-ARs produces beneficial effects on substance-related and addictive disorders; for example, clonidine significantly increases smoking abstinence rates and alleviates alcohol and opioid withdrawal symptoms (Haass-Koffler *et al.* 2018; Srivastava *et al.* 2020; Vanderkam *et al.* 2021). Clonidine and guanfacine have also been used as medications to treat ADHD (Chan *et al.* 2016). Dexmedetomidine, a highly selective a_2-AR agonist that is used in anesthesia in general surgery, may also have a use in management of neuropathic pain (Zhao *et al.* 2020). In general, however, use of a_2-AR agonists in psychiatric disorders may be limited by their potential to cause hypotension and sedation. Antagonists of these receptors, such as clozapine, mirtazapine, and idazoxan, have been used in clinical treatment as antidepressants and antipsychotics; the mechanism of these therapeutic effects has in part been attributed to blockade of a_2-ARs on serotonergic and dopaminergic terminals, resulting in modulation of these systems. In addition, a_2-AR antagonists such as clozapine are not selective for adrenergic receptors and may produce therapeutic effects by virtue of direct interactions with serotonin and dopamine receptors (Langer 2015).

Beta-adrenergic receptors--subdivided into b_1-, b_2-, and b_3-ARs--have the lowest binding affinity for norepinephrine among the different subtypes of noradrenergic receptors. b_1-ARs and b_2-ARs are most prevalent in the CNS, whereas b_3-ARs are mainly expressed in adipose tissue. When b-ARs couple to the Ga_s protein signaling pathway, cAMP levels increase, leading to activation of PKA and producing excitatory cellular effects. b-ARs in the periphery are activated during stress and are responsible for causing increased heart rate (b_1-ARs) and increased pulmonary function (b_2-ARs). b-AR antagonists (e.g., labetalol) include lipophilic molecules that permeate the blood-brain barrier (e.g., propranolol) and hydrophilic molecules with less CNS penetrability (e.g., atenolol, nadolol). b-AR blockers have been used to manage symptoms of agitation and restlessness in schizophrenia and anxiety disorders and to reduce acute performance anxiety; given that improvements were obtained with both blood-brain-permeable (propranolol) and nonpermeable (atenolol, nadolol) antagonists, it is likely that these effects were due to attenuation of the cardiovascular response to catecholamines rather than representing specific CNS effects. In addition to providing these effects, b-AR antagonists may also be useful as adjunctive therapy to treat phobias and to suppress recall of traumatic memories in PTSD (Boyce *et al.* 2021).

Norepinephrine Transporters

As is also the case for the serotonin and dopamine systems, the high-affinity NET is the primary mechanism terminating noradrenergic neurotransmission. Once it is returned to the nerve terminal, norepinephrine is either broken down enzymatically or repackaged into vesicles via VMAT2. NET is located extrasynaptically (Miner *et al.* 2003) and is richly expressed in the cell body region, the locus coeruleus, with lower density in terminal regions, including hippocampus, amygdala, cortex, and hypothalamus (Tejani-Butt 1992). As is the case for SERT and DAT, NET is a symporter, using the sodium gradient generated by the plasma membrane Na^+/K^+ ATPase to carry norepinephrine molecules into the intracellular compartment. Like its monoamine transporter relatives, NET can form oligomers (Jayaraman *et al.* 2021) and is regulated

by a variety of intracellular and extracellular signaling molecules (Mandela and Ordway 2006). First cloned in 1991 (Pacholczyk *et al.* 1991), NET is a member of the SLC6 family and is encoded by the gene *SLC6A2* (for comprehensive reviews of NET structure, function, and regulation, see Mandela and Ordway 2006, Kristensen *et al.* 2011, Ramamoorthy *et al.* 2011, and Pramod *et al.* 2013).

The noradrenergic system plays an important role in control of mood and arousal states, as well as cardiovascular function. Dysfunction in noradrenergic neurotransmission is linked to a number of psychiatric disorders, including depression and ADHD, as well as to orthostatic intolerance and cardiovascular diseases. These disorders are treated (with varying success) with drugs that block NET and lead to increased extracellular norepinephrine, such as desipramine, nisoxetine, reboxetine, atomoxetine, nomifensine, and mazindol (Kristensen *et al.* 2011; Zhou 2004). As noted in previous transporter sections, monoamine transporters are promiscuous (Daws 2009); thus, blockers of NET also serve to increase extracellular serotonin and dopamine to some extent. In addition, OCTs and PMAT are able to transport norepinephrine with low affinity but high capacity, meaning that when extracellular levels of norepinephrine are elevated, OCTs and PMAT can efficiently remove norepinephrine from the extracellular compartment. Studies using OCT2 knockout mice have provided evidence for an important role of this transporter in clearance of norepinephrine and in the antidepressant efficacy of NET-targeting antidepressants such as reboxetine and venlafaxine (Bacq *et al.* 2012). Consistent with these findings, Bowman *et al.* (2020) found that the nonselective OCT blocker decynium-22 enhanced the antidepressant effects of the NET blocker desipramine in mice (see also Daws 2021).

Numerous gene variants of NET have been identified and have been linked to various disorders, although the literature is inconclusive. For example, some studies (e.g., Haenisch *et al.* 2009) have reported evidence suggesting that some variants are associated with depressive disorders, whereas a meta-analysis of existing research reported mixed findings on this association (Zhao *et al.* 2013). NET gene variants have also been associated with ADHD (Hahn *et al.* 2009; Kim *et al.* 2008) and cardiovascular disorders (Hahn *et al.* 2005; Halushka *et al.* 1999; Shirey-Rice *et al.* 2013). NET, like SERT and DAT, continues to be studied both as a source of information on the etiological bases of mental disorders and as a transporter that can be targeted to improve treatment of these disorders.

Cholinergic System

Acetylcholine (ACh) is the neurotransmitter of the parasympathetic nervous system. Indeed, its discovery in 1921 by Otto Loewi as the chemical neurotransmitter from the vagus nerve (hence "Vagusstoff," the name given by Loewi) was the seminal demonstration of chemical synaptic transmission. But ACh also has major roles as a neurotransmitter in the brain, particularly with respect to regulation of learning and memory, motor activity, reward, and cognition. ACh is a choline molecule that has been acetylated at the oxygen atom (see Figure 2-1).

In nerve terminals, ACh is synthesized from acetyl coenzyme A and choline by the enzyme choline acetyltransferase (ChAt). However, the rate of ACh synthesis is limited not by the enzyme activity of ChAt but rather by the uptake of choline into neurons by a high-affinity Na^+-dependent uptake pump. This uptake pump can be blocked by hemicholinium-3, resulting in depletion of ACh. In the CNS, the highest activity of ChAt is found in the caudate nucleus, retina, interpeduncular nucleus, and spinal roots. As discussed elsewhere in this chapter, *transporters* are the primary proteins terminating the activity of most neurotransmitters. By contrast, enzymatic degradation of ACh by the enzyme acetylcholinesterase (AChE) terminates the synaptic activity of ACh, although a high-affinity choline transporter also participates. AChE is one of the most efficient enzymes known; the catalysis of released ACh occurs within a submillisecond time frame. This catalysis is essential in the skeletal neuromuscular junction to allow the next volley of released ACh to trigger a postsynaptic excitatory potential. AChE (Enzyme Commission [EC] number 3.1.1.7) is distinguished from butyrylcholinesterase (BChE; EC 3.1.1.8) by its catalytic selectivity for ACh over butyrylcholine hydrolysis. AChE is synthesized in nerve, muscle, and certain hematopoietic cells. In excitable tissues, AChE is localized on the extracellular surface of both nerve and muscle; in the neuromuscular junction of skeletal muscle, AChE is synthesized by the muscle rather than the nerve cell. Therapies aimed at increasing the function of ACh do so primarily by inhibiting AChE; these drugs are used in the treatment of Alzheimer's disease, myasthenia gravis, glaucoma, smooth muscle atony, and other disorders of autonomic nervous system functions. Such drugs are also used as insecticides and chemical warfare agents (i.e., nerve gases), which cause paralysis of respiratory muscles, primarily the diaphragm, leading to death.

In the brain, cholinergic neurons function both as interneurons (in areas such as the caudate-putamen and nucleus accumbens) and as projection neurons connecting brain areas (e.g., a tract from the septum to the hippocampus). There are eight cholinergic nuclei from which cholinergic neurons originate and send ascending projections to areas such as the nonstriatal telencephalon; descending projections innervate areas such as the pontine and medullary reticular formations, deep cerebellar and vestibular nuclei, and cranial nerve nuclei (Mesulam *et al.* 1984; Satoh and Fibiger 1985). The cholinergic nucleus basalis of Meynert is particularly susceptible to early degeneration in Alzheimer's disease (Theofilas *et al.* 2015). Such observations provide the rationale for cholinergic therapy in mild to moderate Alzheimer's disease.

Cholinergic Receptors

Studies with two alkaloids, nicotine and muscarine, formed the initial basis for subtyping of cholinergic receptors (Dale 1914). Further support for at least two classes of cholinergic receptors, nicotinic and muscarinic, was obtained from studies on the selective effects of the nicotinic ACh receptor antagonist D-tubocurarine on nicotinic responses and of the muscarinic ACh receptor antagonist atropine on muscarinic responses. Five subtypes of muscarinic receptors, m_1-m_5, have been cloned. These receptors are G protein coupled and are widespread in the CNS. The ACh receptor antagonist pirenzepine has high affinity for the m_1 receptor subtype, which predominates in the hippocampus and cerebral cortex, whereas receptors with low affinity for pirenzepine predominate in the cerebellum and brain stem. Muscarinic receptor/G protein interactions can initiate different types of signal transduction mechanisms: 1) inhibition of adenylyl cyclase; 2) stimulation of phosphoinositide hydrolysis via activation of phospholipase C; and 3) regulation of an ion channel, particularly a specific K^+ conductance (Nathanson 1987). Phosphoinositide hydrolysis yields two second messengers, inositol triphosphate and diacylglycerol.

Many of the early psychotherapeutic drugs (e.g., the first-generation antipsychotic chlorpromazine or the TCA imipramine)--and even some of the newer atypical antipsychotics (e.g., clozapine, olanzapine) (Bymaster *et* *al.* 2003)--block muscarinic receptors to produce adverse effects. Such anticholinergic effects may include dry mouth, mydriasis (causing blurred vision), tachycardia, hot and flushed skin, constipation, urinary retention, agitation, and even delirium. A mnemonic for remembering these effects is "red as a beet, dry as a bone, blind as a bat, and mad as a hatter." Patients find these effects quite unpleasant, and they are a common reason that patients discontinue drug use. From a therapeutic perspective, it is now established that muscarinic receptors regulate behaviors such as cognition, learning and memory, reward, and movement, so that there is increasing interest in targeting these receptors to treat various brain disorders, particularly Alzheimer's disease but also schizophrenia (Moran *et al.* 2019).

The nicotinic cholinergic receptor (nAChR) was the first neurotransmitter receptor to be purified to homogeneity. NAChR is an ionotropic receptor with five subunits arranged across the membrane like a doughnut, with the central hole representing the ion channel. Activation of the receptor results in opening of the channel, which has cation selectivity. Neuronal nicotinic receptors contain a and b subunits, with the a subunit having eight different isoforms and the b subunit having three. ACh binding to the a_1 subunit causes activation of the nicotinic receptor. Although ACh is still present at the receptor, the response of neuronal nicotinic receptors diminishes very rapidly, due to the process known as desensitization. Phosphorylation of the receptor by several kinases increases the rapid phase of receptor desensitization. A major function of nAChRs is modulation of excitatory transmission through a presynaptic action. Succinylcholine is a partial agonist of nAChRs and is routinely used during surgery as a muscle relaxant. The arrow-tip poison curare, the active ingredient of which is D-tubocurarine, is an nAChR antagonist. Curare causes death by asphyxia due to paralysis of skeletal muscles. Of interest, it was the use of curare by Claude Bernard in the mid-nineteenth century that first demonstrated a locus of drug action near or at the neuromuscular junction.

Like other drugs of abuse, nicotine stimulates release of dopamine in the nucleus accumbens, and this action is thought to account for its reinforcing properties. The release of dopamine occurs due to stimulation of nicotinic receptors in the VTA and the nucleus accumbens, particularly the $a_4/a_6/b_2$* subtype in the VTA (Picciotto and Mineur 2014). The effective smoking-cessation medication varenicline is a high-affinity partial agonist at this subtype. Varenicline also produces rewarding effects that mitigate the feelings of withdrawal and craving that accompany cessation of smoking (Jordan and Xi 2018).

Glutamatergic System

Glutamate (see Figure 2-1) is the primary excitatory amino acid neurotransmitter in the mammalian CNS and is present in high concentrations throughout the brain. It is responsible for fast excitatory neurotransmission via activity at ionotropic glutamate receptors as well as for initiating intracellular cascades that regulate synaptic plasticity (both long-term potentiation [LTP] and long-term depression [LTD]) and memory. While glutamate plays a central role in excitatory neurotransmission, aberrant glutamatergic signaling is also observed in pathological conditions, and excess glutamate

can be toxic, leading to neuronal death (excitotoxicity). Given the potential for toxicity, glutamate levels in the brain are tightly controlled. As a nonessential amino acid that cannot cross the blood-brain barrier, glutamate is synthesized in the brain, and its metabolism is complex and compartmentalized (Figure 2-14). In contrast to monoamines, whose synthesis and reuptake occur in the neuron, glutamatergic transmission is regulated by astrocytes. Neurons lack the enzyme pyruvate carboxylase and therefore cannot synthesize glutamate through the tricarboxylic acid cycle (also known as the Krebs cycle). Astrocytes generate glutamate via de novo synthesis or by reuptake and recycling of released g-aminobutyric acid (GABA) and glutamate. De novo synthesis requires transamination of the tricarboxylic acid cycle product a-ketoglutarate, which is converted to glutamine by glutamine synthetase, an enzyme predominantly located in astrocytes. Glutamine is then transported (via sodium-coupled neutral amino acid transporters) from the astrocytes to neurons, where it functions as a substrate for the synthesis of both glutamate and GABA (the primary inhibitory amino acid neurotransmitter in the mammalian CNS). In neurons, the enzyme glutaminase converts glutamine back to glutamate, which is then packaged into vesicles via vesicular glutamate transporters (see Figure 2-14). Glutamate released from presynaptic terminals must be rapidly removed to avoid excitotoxicity. The major mechanism for this process is uptake into pre-and postsynaptic neurons as well as uptake by the surrounding astrocytes. The transporters responsible for this uptake are the Na^+-dependent excitatory amino acid transporters ($EAATs_{1-5}$). These transporters are differentially expressed in specific cell types, with $EAAT_1$ and $EAAT_2$ being found primarily in astrocytes and responsible for most of the glutamate reuptake, and $EAAT_3$ being localized on both excitatory and inhibitory neurons. These transporters play a critical role in maintaining extracellular glutamate concentrations and have been shown to be impaired following brain injury (e.g., stroke, trauma). Excitotoxicity is a consequence of sustained glutamatergic transmission and the associated excessive influx of Ca^{2+}. The resulting calcium overload is particularly neurotoxic, leading to activation of catabolic enzymes (e.g., calpain) that trigger a cascade of events leading to cell death (i.e., apoptosis or necrosis) (Lipton 1999).

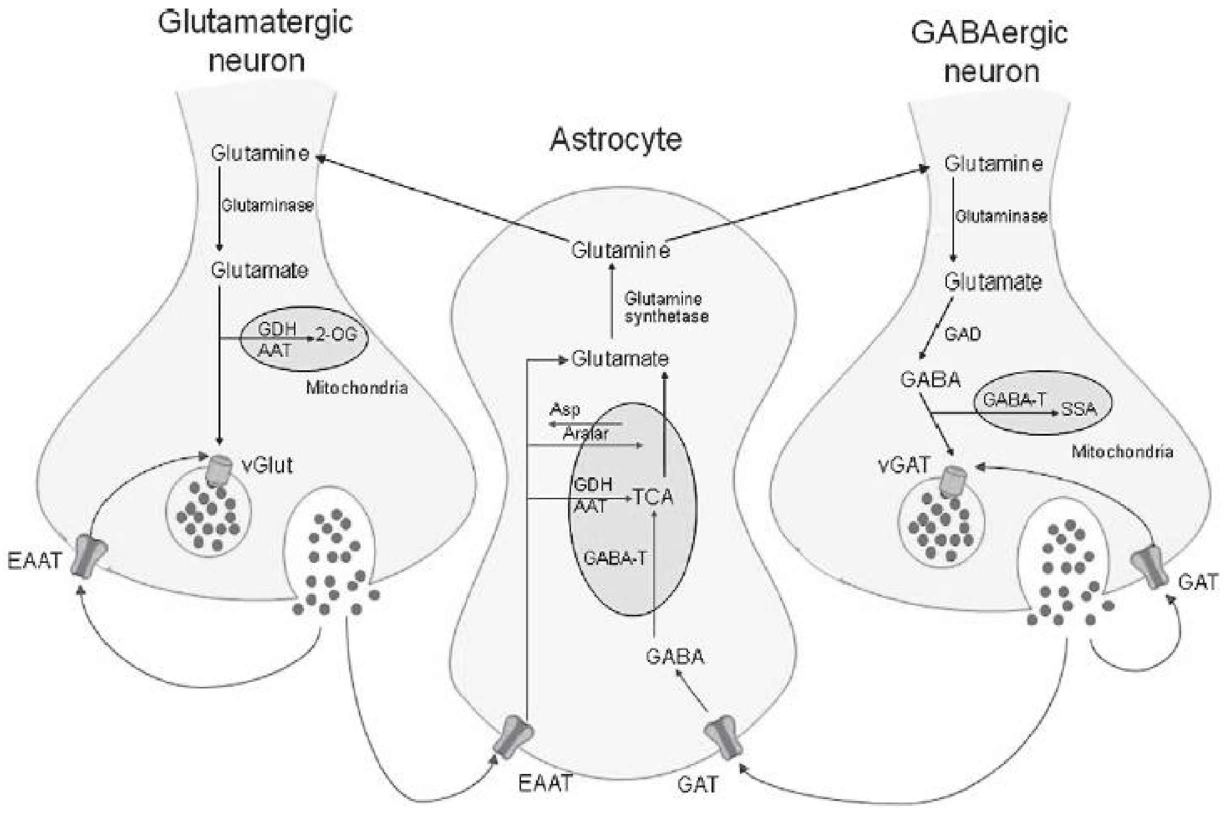

Glutamatergic neuron
Astrocyte
GABAergic neuron
Glutamine
Glutaminase
Glutamate
GDH
AAT
2-OG
Mitochondria
vGlut
EAAT
Glutamine
Glutamine synthetase
Glutamate
Asp
Aralar
GDH
AAT
TCA
GABA-T
GABA
EAAT
GAT
Glutamine
Glutaminase
Glutamate
GAD
GABA
GABA-T
SSA
Mitochondria
vGAT
GAT

FIGURE 2-14. Glutamate and GABA synthesis.

Astrocytes generate glutamate either via de novo synthesis or by recycling of glutamate and GABA, which is converted to glutamate by the enzyme GABA transaminase (GABA-T). Glutamate is converted to glutamine by glutamine synthetase and is transported to neurons, where it functions as a substrate for the synthesis of both glutamate (via glutaminase) and GABA (via glutamic acid decarboxylase). 2-OG = 2-oxoglutarate; AAT = aspartate aminotransferase; Aralar = aspartate-glutamate carrier; Asp = aspartate; EAAT = excitatory amino acid transporter; GAD = glutamic acid decarboxylase; GAT = GABA transporter; GDH = glutamate dehydrogenase; SSA = succinic semialdehyde; TCA = tricarboxylic acid cycle; vGAT = vesicular GABA transporter; vGlut = vesicular glutamate transporter.

Source. Reprinted from Figure 1 (p. 547) of Rowley NM, Madsen KK, Schousboe A, Steve White H: "Glutamate and GABA Synthesis, Release, Transport and Metabolism as Targets for Seizure Control." *Neurochemistry International* 61(4):546-558, 2012 (https://doi.org/10.1016/j.neuint.2012.02.013). Copyright (c) 2012, Elsevier Ltd. Used with permission.

Glutamatergic Receptors

Glutamatergic receptors in the CNS can be classified into two major subtypes: ligand-gated ion channel (ionotropic) receptors and G protein-coupled (metabotropic) receptors (Figure 2-15).

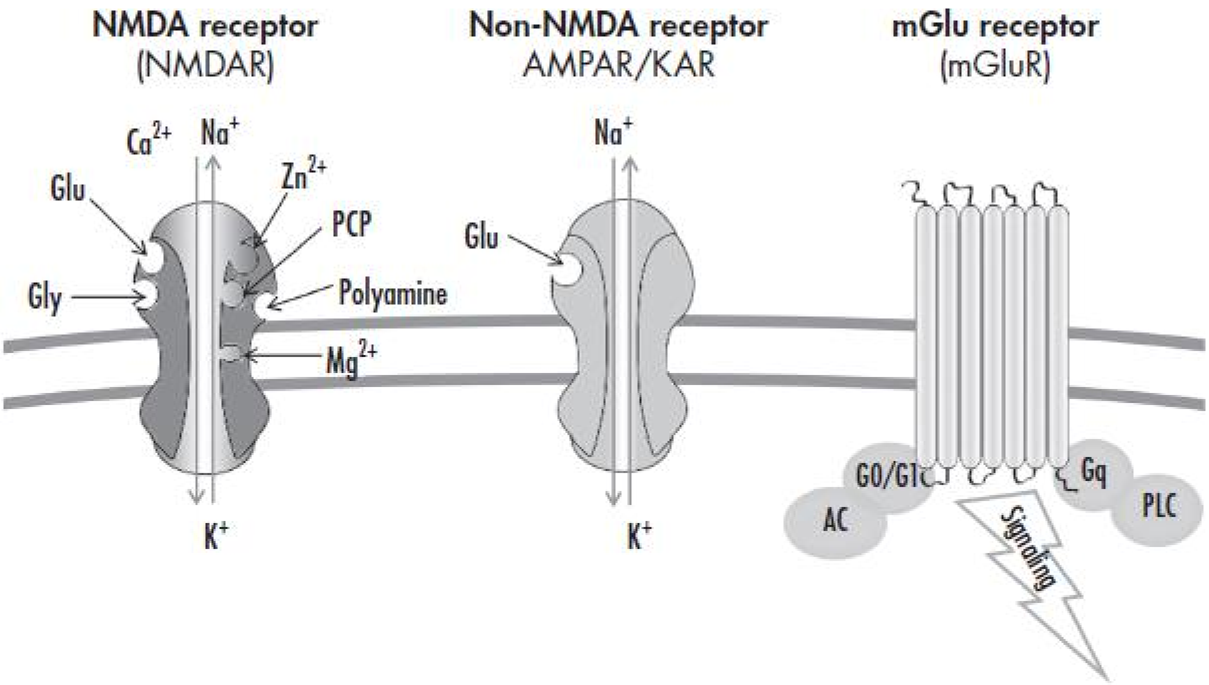


FIGURE 2-15. Glutamatergic receptors.

See Plate 13 to view this figure in color.

Ionotropic glutamate receptors mediate fast excitatory signaling in the brain; however, glutamate also plays a modulatory role through activation of metabotropic receptors. The a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors (AMPAR and KAR) are activated by glutamate and are permeable to Na^+, which results in a rapid, transient depolarization of the plasma membrane. In contrast, *N*-methyl-D-aspartate (NMDA) receptors are more complex, being blocked by Mg^{2+} at hyperpolarized membrane potentials and permeable to Ca^{2+}, permitting activation of various intracellular cascades. AC = adenylyl cyclase; G0/G1, Gq = Gi/o protein a subunits; PLC = phospholipase C; PCP = phencyclidine.

Source. Reprinted from Figure 2 (p. 4) in Kritis AA, Stamoula EG, Paniskaki KA, Vavilis TD: "Researching Glutamate-Induced Cytotoxicity in Different Cell Lines: A Comparative/Collective Analysis Study." *Frontiers in Cell Neuroscience* 9, article 91, 2015 (https://doi.org/10.1146/annurev.pharmtox.011008.145533). Copyright (c) 2015, Kritis, Stamoula, Paniskaki, and Vavilis. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CCBY). The use, distribution, or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution, or reproduction is permitted which does not comply with these terms.

Ionotropic glutamate receptors.

The ionotropic glutamate receptors mediate fast excitatory neuronal transmission in the CNS and can be divided into three distinct classes on the basis of their affinity for three different synthetic ligands: 1) a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), 2) NMDA, and 3) kainate (see Figure 2-15). However, glutamate can bind to all three classes with equal affinity. In the adult mammalian brain, NMDA and AMPA glutamatergic receptors are co-located in approximately 70% of the synapses (Bekkers and Stevens 1989).

AMPA receptors. As is true for all ionotropic glutamate receptors, AMPA receptors are tetrameric, cation-permeable receptors expressed widely throughout the brain. There are four AMPA receptor subunits (GluA1-4), which are assembled as dimers-of-dimers to form a tetrameric receptor. The AMPA receptor is activated by two molecules of glutamate, resulting in a conformational change and rapid channel opening.

Once channels are open, AMPA receptors carry a large inward sodium current that rapidly terminates, resulting in a fast, transient excitatory synaptic signal. It should be noted that the GluA2 subunit possesses a positively charged arginine in the pore-forming region, which prevents Ca^{2+} influx. Because of this characteristic, the majority of GluA2-containing AMPA receptors are considered Ca^{2+}-impermeable. In contrast, AMPA receptors that lack a GluA2 subunit are Ca^{2+}-permeable and may play a role in synaptic plasticity (Isaac *et al.* 2007).

Given the role of AMPA receptors in mediating fast synaptic signaling, changes in the number, location, and phosphorylation of these receptors can produce significant alterations in synaptic strength. The best-known modulation of synaptic strength is the concept of *long-term potentiation* (LTP), a form of cellular memory wherein large, transient increases in excitatory transmission (induced by a variety of electrical, pharmacological, and behavioral mechanisms) lead to an increase in the number of synaptic AMPA receptors and sustained increases in synaptic strength. The converse of LTP is known as *long-term depression* (LTD), in which persistent, low-frequency activation produces a decrease in synaptic strength as a result of a reduction in the number of synaptic AMPA receptors. The mechanisms associated with LTP and LTD are complex; however, the phosphorylation states of the AMPA receptor subunits are directly altered by protein kinases and phosphatases. During LTP, phosphorylation of the receptor subunits enhances the receptor's interaction with proteins that modulate the membrane trafficking and synaptic targeting of the receptor (Malinow and Malenka 2002). Similarly, activation of phosphatases results in the removal of AMPA receptors from the synapse and forms the basis of LTD.

Kainate receptors. The kainate receptor possesses properties similar to those of the AMPA receptors, being a ligand-gated cation channel permeable to Na^+ and K^+. Because of their similarities and the lack of pharmacological tools to distinguish them, kainate and AMPA receptors were previously grouped together and referred to as non-NMDA receptors. The kainate receptors are multimeric assemblies composed of combinations of low-affinity subunits (GluK1, GluK2, and GluK3) and high-affinity subunits (GluK4 or GluK5) (these subunits were formerly known as GluR5, GluR6, GluR7, KA1, and KA2, respectively) that form a tetrameric complex (Mayer 2021). GluK1-GluK3 may form functional homomeric or heteromeric receptors, whereas GluK4 and GluK5 form functional receptors only when paired with the GluK1-GluK3 subunits. Until recently, relatively little was known about the functional and physiological roles of kainate receptors. Based on the observation that intraperitoneal injections of kainate produce severe seizures and neurotoxicity in preclinical models, the kainate receptors have classically been implicated in epileptogenesis (Ben-Ari and Cossart 2000). These seizurogenic properties suggest that kainate receptor antagonists might have clinical utility as anticonvulsants and neuroprotectants. Indeed, preclinical studies have demonstrated that kainate receptor antagonists display antiepileptic activity in preclinical models of epilepsy; however, the efficacy of kainate receptor antagonists has not yet been examined clinically due to a lack of appropriate pharmacological compounds.

Kainate receptors are widely distributed throughout the brain, with high expression observed throughout the hippocampus, a key structure involved in memory consolidation and a site of pathology in temporal lobe epilepsy. Within the hippocampus, GluK1 subunits are highly expressed on GABAergic interneurons, whereas GluK2 subunit-containing kainate receptors are primarily located on excitatory pyramidal neurons (Falcon-Moya *et al.* 2018). This differential localization allows kainate receptors to have fine control over neural circuits in the hippocampus. In addition, the kainate receptor appears to have a unique signaling mechanism, other than its ionotropic effects, by which kainate regulates hippocampal function. This noncanonical signaling takes place by means of an unconventional metabotropic mechanism involving G protein signaling. Specifically, presynaptic inhibition of GABA release by kainate is dependent on G protein activation and PKC activity. A similar noncanonical mechanism was observed in dorsal root ganglion neurons, where it was demonstrated that the effects of kainate are independent of ion channel function (Rozas *et al.* 2003). Although this metabotropic effect of kainate receptor function is relatively well established, the molecular mechanisms underlying noncanonical signaling require further elucidation.

The advent of genetic knockout mice has enabled investigation of the biological functions of the kainate receptor, even when pharmacological tools are lacking. For example, in a series of studies investigating the role of GluK2 in rodent behaviors, GluK2 knockout mice were hyperactive and extremely aggressive, took more risks, and consumed excessive amounts of sweetened water (Shaltiel *et al.* 2008). This phenotype was consistent with phenotypes of mania observed in patients with bipolar disorder. Interestingly, some of the aberrant behaviors observed in the GluK2 knockout mice were reversed by long-term lithium administration, suggesting the potential involvement of kainate receptors in the pathophysiology of bipolar disorder (Shaltiel *et al.*

2008). Indeed, polymorphisms associated with GluK2 (6q16.3-q21) may contribute to an increased risk of mood disorders.

***NMDA receptors*.** As is also the case for the AMPA and kainate receptors, NMDA receptors are tetrameric, cation-permeable ionotropic glutamate receptors expressed widely throughout the brain. Functional NMDA receptors are typically composed of two GluN1 and two GluN2 subunits; however, there are one GluN1, four GluN2, and two GluN3 subunit-encoding genes, and alternative splicings of each gene can produce additional variants. The NMDA receptor is activated by two molecules of glutamate, and this activation requires the presence of the co-agonist glycine (or D-serine). The binding site for glutamate has been localized to the GluN2 subunit, and the site for the co-agonist glycine has been localized to the GluN1 subunit. Activation of the NMDA receptor results in a conformational change and the opening of a nonselective cation channel, allowing a voltage-dependent flow of sodium (Na^+) and calcium (Ca^{2+}) ions into the cell. It should be noted that binding of both glutamate and glycine is not sufficient for ion flow across the NMDA receptor channel because at resting membrane potential, the NMDA ion channel is blocked by magnesium (Mg^{2+}) ions. Like Ca^{2+}, Mg^{2+} is a divalent cation that is present at millimolar concentrations in the extracellular space. Upon NMDA receptor opening, Mg^{2+} enters the NMDA receptor pore, but unlike Ca^{2+} ions, Mg^{2+} ions bind tightly and prevent ion flow. This Mg^{2+} blockade is removed only when the membrane is sufficiently depolarized (e.g., by activation of AMPA and kainate receptors on the same postsynaptic neuron). As a result, the NMDA receptor acts as a molecular coincidence detector, requiring both a sufficiently strong depolarization and the synaptic release of glutamate for the NMDA receptor channel to open and permit the entry of both Na^+ and Ca^{2+} (Nowak *et al.* 1984) (see Figure 2-15). Furthermore, given their high Ca^{2+} permeability, NMDA receptors induce long-lasting alterations in synaptic strength and are required for classical LTP.

Given the prominent role of NMDA signaling in cellular memory (LTP), this receptor has been proposed as a potential therapeutic target for Alzheimer's disease. Indeed, one of the five prescription drugs approved by the FDA to treat the symptoms of Alzheimer's disease is memantine, an

NMDA receptor antagonist. Given that NMDA receptor antagonists block LTP and impair memory, it might seem counterintuitive that these drugs are used in Alzheimer's disease. However, memantine is a low-affinity, voltage-dependent, noncompetitive antagonist of NMDA receptors with fast on/off kinetics that inhibits excessive calcium influx induced by chronic overstimulation of the NMDA receptor. These unique pharmacological properties mean that memantine can inhibit pathological alterations in NMDA receptor function while preserving normal physiological activity. Maintenance of physiological activity is essential to protect against the negative effects on learning and memory observed with high-affinity NMDA receptor antagonists (Reisberg *et al.* 2003).

In addition to their effects on learning and memory, NMDA receptor antagonists also possess hallucinogenic properties. The hallucinogens phencyclidine and ketamine bind within the channel pore as noncompetitive receptor antagonists to inhibit NMDA receptor channel function. Moreover, in clinical studies, ketamine has been shown to induce schizophrenia-like symptoms in healthy people and to induce psychosis in schizophrenic patients. This psychotomimetic effect of NMDA receptor antagonists led to the NDMA hypothesis of schizophrenia, which posits that decreases in NMDA receptor function contribute to the pathophysiology of the disorder (Goff and Coyle 2001). This hypothesis is further supported by the observation that individuals with autoimmune antibodies to the NMDA receptor (anti-NMDA receptor encephalitis) display psychosis. This NMDA receptor hypofunction hypothesis suggests novel targets for therapeutic interventions for patients with schizophrenia. Therapeutic targets that augment NMDA receptor function are largely compounds that target the glycine co-agonist site. Direct glycine site agonists include glycine, D-serine, and D-cycloserine; indirect agonists include agents that block glycine degradation (D-amino acid oxidase [DAAO] inhibitors) or glycine uptake (glycine transporter-1 [GlyT-1] blockers). Unfortunately, the NMDA receptor-modulating drugs showed only small to moderate effects in treating negative symptoms and did not improve cognition in patients with schizophrenia (Buchanan *et al.* 2007).

Drugs used to treat major depressive disorder are moderately effective (effect sizes of 0.4-0.5), and most target noradrenergic and/or serotonergic neurotransmission (see sections on serotonin and norepinephrine transporters in this chapter). Furthermore, approximately 15%-25% of patients treated with such drugs have essentially no response and are considered to have treatment-resistant depression (TRD) (Nemeroff 2007). This high incidence of TRD has led to an examination of whether drugs that target different neuronal systems might be more effective, act faster, and/or be more useful in treating depression compared with current antidepressant drugs that target only monoamine neurotransmission. The "glutamate theory" of depression led to the suggestion that NMDA receptor antagonists may represent a novel therapeutic target for treatment. Preclinical studies have consistently demonstrated the efficacy of NMDA receptor antagonists in behavioral models with predictive validity of an antidepressant response. Further evidence supporting NMDA receptor antagonists as a therapeutic approach to depression was obtained in 2000, when ketamine, an NMDA receptor antagonist, was found in an open study to produce an antidepressant effect when administered to depressed patients (at subanesthetic doses) (Berman *et al.* 2000). Subsequent randomized double-blind studies also demonstrated a rapid antidepressant effect of ketamine, with high response rates even in patients with TRD. The efficacy in clinical trials led to FDA approval of the *S*(+)-enantiomer of ketamine, esketamine (sold under the brand name Spravato), for use in TRD. Given its rapid antidepressant action, esketamine was subsequently examined as a potential therapy for patients with suicidal ideation, and in 2020 esketamine was approved for use in the short-term treatment of suicidal thoughts. It should be noted that there are serious drawbacks to the use of this drug. Because of its potential to produce transient blood pressure and heart rate changes, esketamine is available only through a restricted program (U.S. Food and Drug Administration 2022). It can be dispensed only in health care settings that have been certified by this program, and only to patients who are enrolled in the program. Finally, doses must be administered under controlled conditions, with the patient being directly observed by a health care provider and monitored for at least 2 hours after administration. In addition to its effects on blood pressure and heart rate, esketamine can produce acute psychotomimetic effects, including hallucinations and dissociative effects. These effects, as well as ketamine's reinforcing properties, contribute to its abuse potential, which further complicates its use for the treatment of depression. Consequently, a significant amount of research is being examined to identify drugs that produce ketamine's beneficial clinical effects without also producing adverse effects.

Metabotropic glutamate receptors. The discovery of metabotropic glutamate receptors (mGluRs) drastically altered the traditional view of glutamatergic neurotransmission as mediating fast synaptic neurotransmission. Indeed, mGluRs can modulate fast glutamatergic signaling in a manner previously associated with monoamines and other neuromodulators. Thus, mGluRs provide a mechanism by which glutamate can modulate or fine-tune activity at the same synapses at which it elicits fast synaptic responses. The mGluRs are GPCRs, of which eight subtypes have been cloned, with multiple splice variants that are differentially expressed in distinct cell types throughout the CNS. These eight subtypes have been categorized into three subgroups (groups I, II, and III) largely based on the signaling transduction pathways that they activate (Table 2-4). Group I includes mGluRs 1 and 5, Group II includes mGluRs 2 and 3, and Group III includes mGluRs 4, 6, 7, and 8 (Niswender and Conn 2010).

TABLE 2-4. Metabotropic glutamate receptors

Subgroup	Subtype	CNS expression	Synaptic localization	Signaling
Group I	mGluR1	Neurons (widespread)	Predominantly postsynaptic	PLC (activation)

Note. cGMP = cyclic guanosine monophosphate; MAP = mitogen-activated protein; PDE = phosphodi-esterase; PLC = phospholipase C.

Source. Adapted from Niswender CM, Conn PJ: "Metabotropic Glutamate Receptors: Physiology, Pharmacology, and Disease." *Annual Review of Pharmacology and Toxicology* 50(1):295-322, 2010 (https://doi.org/10.1146/annurev.pharmtox.011008.145533). Copyright (c) 2010, Annual Reviews.

Subgroup	Subtype	CNS expression	Synaptic localization	Signaling
	mGluR5	Astrocytes (mGluR5)		Adenylyl cyclase (activation) MAP kinase (activation)
Group II	mGluR2	Neurons (widespread) Astrocytes	Presynaptic and postsynaptic	Adenylyl cyclase (inhibition)
	mGluR3			K^+ channels (activation) Ca^{2+} channels (inhibition)
Group III	mGluR4	Neurons (widespread)	Predominately postsynaptic	Adenylyl cyclase (inhibition)
	mGluR6	Cerebellum (high; GluR6)	Active zone of presynaptic (mGluR7)	K^+ channels (activation)
	mGluR7	Retina (mGluR7)		Ca^{2+} channels (inhibition) cGMP PDE (activation; mGluR6)

Note. cGMP = cyclic guanosine monophosphate; MAP = mitogen-activated protein; PDE = phosphodi-esterase; PLC = phospholipase C.

Source. Adapted from Niswender CM, Conn PJ: "Metabotropic Glutamate Receptors: Physiology, Pharmacology, and Disease." *Annual Review of Pharmacology and Toxicology* 50(1):295-322, 2010 (https://doi.org/10.1146/annurev.pharmtox.011008.145533). Copyright (c) 2010, Annual Reviews.

Group I mGluRs. Group I mGluRs (which include mGlu1 and mGlu5 receptors) couple to G_q/G_{11} and activate PLC, resulting in generation of IP_3

and diacylglycerol. Thus, receptor stimulation leads to mobilization of intracellular calcium and activation of PKC. Group I mGluRs are often localized postsynaptically, and their activation leads to cell depolarization and increases in neuronal excitability. mGlu1 receptors are concentrated in perisynaptic and extrasynaptic areas, whereas mGlu5 receptors appear synaptic, functionally interacting with NMDA receptors in the postsynaptic density. Given their interaction with NMDA receptors, mGlu5 receptors have been associated with learning and memory. Indeed, mGluR5 knockout mice show memory impairments on specific behavioral tasks and reduced plasticity in the hippocampus. Whereas AMPA receptor signaling appears normal in these mice, NMDA receptor-mediated LTP is attenuated (Jia *et al.* 1998). Research on allosteric modulators for the mGluR5 receptor has yielded several compounds with potential clinical utility. PAMs may have utility for the treatment of cognitive deficits, including those seen in schizophrenia. Indeed, given that mGluR5 PAMs display robust antipsychotic-like effects and improve cognitive function in animal models, they may possess utility as novel antipsychotic and cognition-enhancing agents. In addition to the potential utility of mGluR5 PAMs in treating psychiatric disorders, NAMs or antagonists have been developed for the treatment of anxiety disorders and fragile X syndrome (FXS). Aberrant amygdala excitability has been linked to anxiety disorders, and attenuation of glutamatergic transmission (by decreasing mGluR5 activity) has been demonstrated to produce anxiolytic effects in rodent models. The proposed interaction between mGluR5 and FXS, a genetic condition that causes a range of developmental problems including intellectual developmental disorder, is based on the finding that the lack of fragile X mental retardation protein (FMRP) results in excessive glutamatergic signaling

via mGluR5 (Dolen *et al.* 2007). Thus, mGluR5 NAMs may represent a novel therapy for FSX. This hypothesis is supported by findings from preclinical research and clinical trials with the selective mGluR5 NAM fenobam (Berry-Kravis *et al.* 2009). Fenobam was developed in the 1970s as an anxiolytic; however, dose-limiting effects on memory decreased its utility. A pilot clinical study did not find major safety concerns with fenobam in FXS and suggested potential clinical improvements after a single dose that warrant further investigation (Berry-Kravis *et al.* 2009).

Group II mGluRs. Group II mGluRs include mGlu2 and mGlu3 receptors and are characterized as inhibiting adenylyl cyclase, but like many G_i-coupled receptors, they also regulate ion channel function. These receptors are largely presynaptic and negatively modulate glutamate and GABA neurotransmission. As detailed above (see "Group I mGluRs"), aberrant activity in the amygdala is associated with anxiety; thus, decreasing glutamatergic transmission in this region would likely produce an anxiolytic effect. This idea led to the development of group II selective mGlu2/3 receptor agonists that displayed robust anxiolytic effects in preclinical models. However, the efficacy of benzodiazepines for anxiety and the side effects associated with early mGlu2/3 receptor agonists limited the investigation of Group II mGluRs as anxiolytics. The hypothesis that aberrant glutamatergic signaling may also contribute to the symptoms of schizophrenia led to the development of pomaglumetad (LY-404039) and its prodrug (LY2140023) as potential antipsychotics. An initial Phase II clinical trial showed that LY2140023, taken twice daily for 4 weeks, improved schizophrenia symptoms, and the drug was heralded as a breakthrough, being potentially the first nondopaminergic antipsychotic (Patil *et al.* 2007). Unfortunately, development of LY2140023 as a treatment for schizophrenia was discontinued in 2012, when later studies found that its antipsychotic effect did not separate from placebo (Kinon *et al.* 2011). However, this compound was licensed to another pharmaceutical company, which reported that a meaningful subset of patients showed significantly improved outcomes; the company plans to utilize genetic biomarkers as a companion diagnostic to screen for appropriate patient subsets in future clinical trials of antipsychotic efficacy (see www.denovobiopharma.com).

Group III mGluRs. Group III mGluRs include mGlu4, mGlu6, and mGlu7 receptors and are similar to group II mGluRs in that they are coupled predominantly to $G_{i/o}$ proteins, leading to inhibition of adenylyl cyclase and regulation of ion channel function. Preclinical studies suggest that group III mGluRs are largely located presynaptically and decrease neurotransmitter release. Group III mGluRs are highly expressed throughout the basal ganglia, and the mGlu4 subtype is highly localized at striatopallidal synapses. This localization within the basal ganglia has led to the suggestion that group III mGluR agonists (or PAMs) might be effective in treating Parkinson's disease (Amalric *et al.* 2013). Activation of mGlu4 receptors reduces aberrant GABAergic transmission at the striatopallidal synapses in patients with Parkinson's disease. Furthermore, highly selective mGluR4 PAMs, such as PHCCC (*N*-phenyl-7-(hydroxyimino)cyclopropa[*b*]chromen-1a-carboxamide), display robust antiparkinsonian effects in rodent models. In addition, activation of mGlu4 receptors has also been shown to be neuroprotective in animal models of Parkinson's disease, a finding that suggests additional benefits for this class of compound (Amalric *et al.* 2013).

Glutamatergic (excitatory amino acid) transporters. As discussed earlier (see "Glutamatergic System"), glutamate transporters, also commonly known as excitatory amino acid transporters (EAATs), are the primary mechanisms terminating glutamatergic neurotransmission. Located pre-and postsynaptically as well as on astrocytes, glutamate transporters are essential for the rapid removal of synaptic and extracellular glutamate, thereby exerting tight control over glutamatergic neurotransmission and preventing neuronal death due to excitotoxicity (Lipton 1999). As is the case for the SLC6 family of transporters, EAATs use the free energy of ion gradients to carry glutamate into cells. In general, mammalian EAATs carry one glutamate molecule along with three sodium ions and one proton into the cytoplasm. There are five EAAT isoforms belonging to the solute carrier 1 (SLC1) family. EAAT1 (SLC1A3; also known as GLAST-1 [GLutamate ASpartate Transporter 1]) and EAAT2 (SLC1A2; also known as GLT-1 [GLutamate Transporter 1]) are located predominantly on astrocytes. EAAT1 is richly expressed in cerebellum, whereas EAAT2 is more diffusely expressed in the brain but is especially dense in hippocampus. EAAT3 (SLC1A1) and EAAT4 (SLC1A6) are located exclusively on neurons. EAAT4 is expressed in cerebellar Purkinje neurons, whereas EAAT5 (SLC1A7) is found only on neurons and Muller cells in the retina.

EAAT2 and EAAT1 reportedly make up 80% and 20% of cell-surface EAATs in the hippocampus, respectively (Holmseth *et al.* 2012), and EAAT2 mediates more than 90% of glutamate uptake in the CNS (Furness *et al.* 2008). EAAT2 and EAAT1 are also critical for normal brain development (Matsugami *et al.* 2006). Because of these important roles in CNS function, EAAT2, and to a lesser extent EAAT1, has been implicated in psychiatric disorders, including substance use disorders. (For comprehensive reviews of glutamate transporter structure, function, and regulation, see Jiang and Amara 2011, Sery *et al.* 2015, and Ryan *et al.* 2021.)

Dysfunction of glutamatergic signaling as well as glial dysfunction are thought to be involved in the etiologies of psychiatric disorders such as depression and schizophrenia (Nakagawa and Kaneko 2013). EAAT2 and EAAT1 have therefore been proposed as targets for novel therapeutics to treat these disorders. In general, EAAT2 and EAAT1 appear to be reduced in patients with depression or schizophrenia; mood stabilizers, such as sodium valproate, and antidepressants, such as fluoxetine (an SSRI) and tranylcypromine (an MAOI), can restore expression of these transporters. However, it is important to keep in mind that postmortem changes associated with patient demographics, long-term medication use, and suicide must be taken into account when considering these findings (for a review, see Parkin *et al.* 2018). A systematic review of the literature by Blacker *et al.* (2020) found that EAAT2 expression was decreased by chronic stress and that inhibition of EAAT2 promoted depressive-like behaviors in rodents. Consistent with findings in rodent studies, depression in humans has been associated with decreased EAAT2. Numerous gene variants for EAAT2 and EAAT1 have been identified (e.g., Poletti *et al.* 2018, 2019; Veldic *et al.* 2019), with some evidence pointing to associations with certain depression subtypes, schizophrenia, and deficits in cognitive function, memory, and executive function, as well as associations with suicide and response to drugs (for a review, see Blacker *et al.* 2020). A wide range of abused drugs, including amphetamines, cannabinoids, cocaine, ethanol, opioids, and nicotine, reduce EAAT2 expression and glutamate uptake. A number of preclinical and clinical studies (reviewed by Roberts-Wolfe and Kalivas 2015) have shown that pharmacological restoration of EAAT2 expression and function with *N*-acetylcysteine (a precursor to glutathione that is used to treat acetaminophen overdose) or ceftriaxone (a b-lactam antibiotic) may be a promising strategy for treating patients with a substance use disorder.

Finally, a less-studied transporter, the cystine/glutamate antiporter (also known as system $x_c^{[?]}$), is responsible for release of glutamate primarily from non-neuronal cells, thereby contributing to glutamate receptor activation. The cysteine/glutamate antiporter has been implicated in substance use disorders, schizophrenia, and neurodegenerative disorders, making it a putative novel target for therapeutic interventions (reviewed in Bridges *et al.* 2012).

Glycine

Glycine is a nonessential amino acid (see Figure 2-1) neurotransmitter in the CNS, serving as a co-agonist for NMDA receptor activation as well as an agonist at the glycine receptor, predominantly in the brain stem and spinal cord. Glycine may be produced in the CNS through a number of pathways; however, the most prominent is the synthesis of glycine from serine by the mitochondrial isoform of the enzyme serine hydroxymethyltransferase. Glycine is found in higher concentrations in the spinal cord than in the rest of the CNS, and it acts as an inhibitory neurotransmitter. Found in the seeds of the strychnine tree (*Strychnos nux-vomica*), strychnine is a highly toxic glycine receptor antagonist that can induce severe muscle rigidity and spasm, leading to respiratory failure and death. As discussed earlier (see "NMDA receptors"), glycine is critical for NMDA receptor channel opening; however, this effect is strychnine-insensitive, which suggests that glycine's actions on NMDA receptor function are different from its actions in the spinal cord, where glycine's inhibitory effect is blocked by strychnine. Indeed, glycine receptors have been cloned and have been demonstrated to be ionotropic receptors that generally produce effects via Cl[?]-mediated hyperpolarization.

Glycine Receptors

Receptors of the glycine family are tetramers, arranged as five subunits, with four known isoforms of the a subunit (a1-4) and a single b subunit. Each heteromeric receptor is thought to contain either three a subunits and two b subunits or four a subunits and one b subunit. Given the localization of glycine receptors within the spinal cord, it is perhaps not surprising that most research to date has focused on developing glycine receptor-targeted treatments for chronic pain. Although it is evident that glycine receptors are present on motoneurons, identification of the a3 subunit in sensory divisions of the spinal cord involved in pain processing has led to increased research efforts targeting a3-containing glycine receptors (Harvey *et al.* 2009). Development of glycine receptor a3 subunit knockout mice has permitted investigation of the effects of glycine in the absence of subtype-selective ligands. Notably, the a3-containing glycine receptors appear to play a central role in inflammatory pain while being less relevant to other pain states (e.g., neuropathic pain) (Harvey *et al.* 2009).

Glycine Transporters

Two subtypes of glycine transporter, GLYT1 and GLYT2, clear glycine from synapses and extracellular fluid. GLYT1 is found predominantly on astrocytes but also on neuronal elements including glutamatergic terminals and postsynaptic membranes. In contrast, GLYT2 is found exclusively on presynaptic glycinergic terminals. GLYT1 is widely expressed in the brain but is most dense in the cerebellum, substantia nigra, brain stem, cortex, and hippocampus. GLYT2 is expressed predominantly in the cerebellum and brain stem (Cubelos *et al.* 2005; Zafra *et al.* 1995). Glycine taken up into nerve terminals is repackaged into vesicles by the vesicular inhibitory amino acid transporter (VIAAT), also known as the vesicular GABA transporter (vGAT). Because glycine and GABA share this vesicular transporter, both neurotransmitters can be released from the same vesicles. GLYT1 and GLYT2 can be pharmacologically distinguished by *N*-

methylglycine (sarcosine), which inhibits GLYT1 but not GLYT2. These two glycine transporter subtypes belong to the SLC6 family and are encoded by the genes *SLC6A9* and *SLC6A5*. Like other members of the SLC6 family, glycine transporters use the free energy created by the sodium gradient maintained by the plasma membrane Na$^+$/K$^+$ ATPase to transport glycine molecules into the cytosolic compartment. (For comprehensive reviews of glycine transporter structure, function, and regulation, see Kristensen *et al.* 2011 and Zafra *et al.* 2008.)

Both glycine transporters have been linked to the etiology and/or the treatment of a number of psychiatric disorders, including schizophrenia, depression, OCD, and neurocognitive disorders, as well as to alcohol use disorder, epilepsy, pain, breathing disorders, and hyperekplexia (a startle disease) (for a review, see Harvey and Yee 2013). Interestingly, several mutations in the gene encoding GLYT2 have been identified in patients with hyperekplexia, a rare hereditary neurological disorder that may affect infants (either as newborns [neonatal] or prior to birth [in utero]) as well as children and adults. Individuals with this disorder have an excessive startle reaction (eye blinking or body spasms) to sudden, unexpected noise, movement, or touch. Most mutations were loss-of-function mutations (Eulenburg *et al.* 2006; Rees *et al.* 2006). Subsequent studies have provided evidence that loss-of-function (or damaging) GLYT1 gene variants may afford protection against schizophrenia, although further studies are needed to confirm these initial findings (Curtis 2020). Of the two transporter types, GLYT2 has garnered the most attention as a potential target for the treatment of pain, although GLYT1 also appears to be a putative target for pain, as well as for a number of the above-mentioned pathologies (Harvey and Yee 2013). Prominent among these, GLYT1 is under active investigation for the treatment of schizophrenia (Cioffi 2018; Cioffi and Guzzo 2016; Singer *et al.* 2015). Despite the promise of GLYT1 inhibitors as therapeutics for schizophrenia and related psychiatric disorders, no compounds have gone further than Phase III clinical trials at this time.

GABAergic System

GABA is the primary inhibitory amino acid neurotransmitter (see Figure 2-1) in the mammalian CNS and, as is the case for glutamate, is present in high concentrations throughout the brain. GABA is responsible for inhibitory neurotransmission via activity at both ionotropic and metabotropic GABA receptors. An imbalance between excitatory and inhibitory transmission contributes to the pathophysiology of a number of psychiatric disorders, including autism spectrum disorder and schizophrenia (Sohal and Rubenstein 2019).

GABA shares the same complex and compartmentalized biosynthetic pathway as glutamate, where glutamine is synthesized and transported from astrocytes to neurons via a sodium-coupled neutral amino acid transporter. In neurons, the enzyme glutaminase converts glutamine to glutamate, which is then converted to GABA by the enzyme glutamic acid decarboxylase (GAD). GAD exists in two isoforms, GAD67 and GAD65 (named for their molecular weights), which are encoded by distinct genes (*GAD1* and *GAD2*). GABA is packaged for release by vesicular GABA transporters. In common with the other amino acid transmitters, GABA's actions are terminated by high-affinity Na^+-dependent excitatory amino acid transporters found in neurons and glia. Neuronal uptake permits immediate repackaging of GABA into vesicles for release. Within astrocytes, GABA is first converted back into glutamate by the enzyme GABA transaminase (GABA-T) via a pathway known as the "GABA shunt." Glutamate is then converted to glutamine by the enzyme glutamine synthase, and glutamine diffuses back into the neuron, completing the cycle (Figure 2-16).

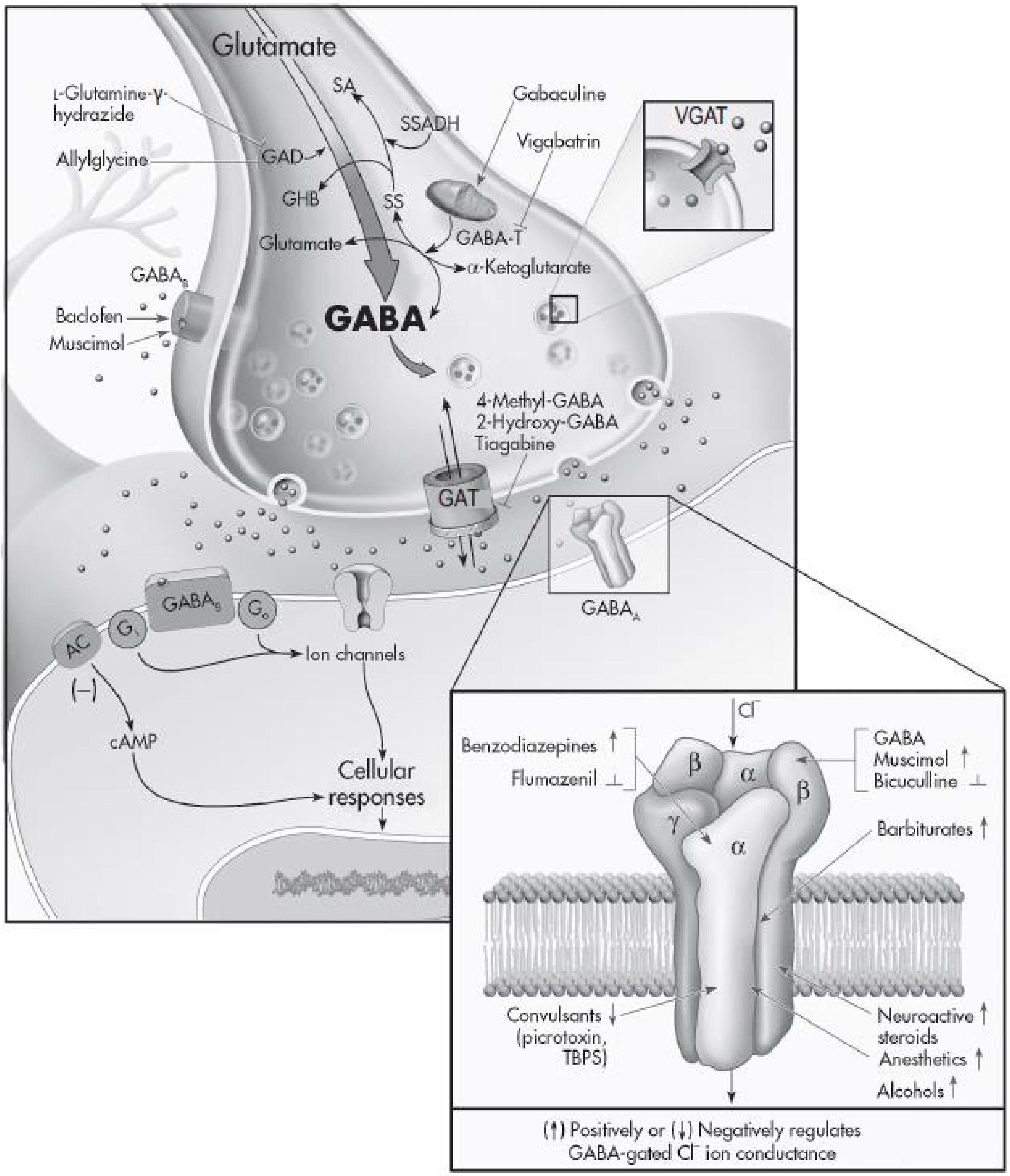

Glutamate
L-Glutamine-γ-hydrazide
Allylglycine
GAD
SA
SSADH
GHB
SS
Gabaculine
Vigabatrin
VGAT
Glutamate
GABA-T
α-Ketoglutarate
GABA_B
Baclofen
Muscimol
GABA
4-Methyl-GABA
2-Hydroxy-GABA
Tiagabine
GAT
GABA_B
G_i
G_o
AC
(–)
cAMP
Ion channels
Cellular responses
GABA_A
Cl⁻
Benzodiazepines ↑
Flumazenil ⊥
GABA
Muscimol ↑
Bicuculline ⊥
β
α
β
γ
α
Barbiturates ↑
Convulsants ↓ (picrotoxin, TBPS)
Neuroactive steroids ↑
Anesthetics ↑
Alcohols ↑
(↑) Positively or (↓) Negatively regulates GABA-gated Cl⁻ ion conductance

FIGURE 2-16. The GABAergic system.

See Plate 14 to view this figure in color.

GABA is synthesized from glutamate by the enzyme glutamic acid decarboxylase (GAD) and, following release, binds to both ionotropic GABA_A and metabotropic GABA_B receptors. GABA_A receptors are ligand-gated $\text{Cl}^{[?]}$ channels that hyperpolarize the cell and mediate fast inhibitory signaling in the brain. $GABA_A$ receptors are heteropentameric receptor complexes, composed of numerous subunit isoforms that determine agonist affinity, allosteric modulation, and other channel properties. Note that GABA transporters are located both synaptically (as shown in figure) and extrasynaptically. AC = adenylyl cyclase; cAMP = cyclic adenosine monophosphate; GABA-T = GABA transaminase; GAT = GABA transporter; TBPS = *t*-butylbicyclophosphorothionate; VGAT = vesicular GABA transporter.

Source. Reprinted from Figure 2-8 (pp. 94-95) in Drazinic CM, Szabo ST, Gould TD, Manji HK: "Neurotransmitters and Receptors in Psychiatric Disorders," in *The American Psychiatric Association Textbook of Psychopharmacology*, 5th Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Association Publishing, 2017, pp. 45-116. Copyright (c) 2017, American Psychiatric Association. Used with permission.

In the brain, GABAergic neurons display robust heterogeneity, with numerous subpopulations distinguished by a combination of morphological, physiological, and molecular characteristics. Within cortical microcircuits, these GABA neuron subtypes differentially regulate excitatory/inhibitory transmission. Two subclasses of GABA neurons that have gained significant attention for their potential role in psychiatric disorders are the parvalbumin-containing interneurons and the somatostatin-containing interneurons, both of which have been found to be selectively decreased in the brains of patients with schizophrenia, autism spectrum disorder, or Alzheimer's disease. These interneuron populations are distinct in terms of both anatomy and neurophysiology (Lewis *et al.* 2005). For example, parvalbumin-containing neurons display a fast firing pattern and synapse on the soma and initial segment, which makes them well situated to regulate phasic pyramidal cell output. By contrast, somatostatin-containing

neurons display a slow firing pattern and synapse on more distal dendrites of the pyramidal neuron, where they play a more modulatory role. Interestingly, parvalbumin and somatostatin interneurons share a similar developmental trajectory from common precursors in the embryonic medial ganglionic eminence, which may explain why developmental disorders such as schizophrenia display selective decreases in these interneurons. A decrease in interneuron function is thought to contribute to the aberrant cortical and hippocampal activity associated with specific symptom domains in patients with schizophrenia.

GABA Receptors

GABA receptors in the CNS can be classified into two major subtypes: ligand-gated ion channel (ionotropic) receptors and G protein-coupled (metabotropic) receptors.

Ionotropic GABA receptors. The ionotropic GABA receptors (see Figure 2-16) mediate fast inhibitory neuronal transmission in the CNS. The $GABA_A$ receptor is the more prevalent of the GABA receptors and, as a result, has been extensively studied and characterized. Structurally, $GABA_A$ receptors are members of the superfamily of pentameric ligand-gated ion channels, which also include nicotinic ACh receptors, serotonin type 3 ($5\text{-}HT_3$) receptors, and glycine receptors and which differ from the tetrameric ionotropic glutamate receptors. The $GABA_A$ receptor is a ligand-gated $Cl^{[?]}$ channel that generally produces effects via $Cl^{[?]}$-mediated hyperpolarization of the neuron (see Figure 2-16). This receptor is a heteropentameric complex composed of numerous subunit isoforms that determine agonist affinity, allosteric modulation, and other channel properties. The $GABA_A$ receptor shows enormous heterogeneity, being composed of a combination of at least 19 cloned subunits in designated subunit families (a1-6, b1-3, g1-3, d, e, th, p, and r1-3) (Sigel and Steinmann 2012). The most common $GABA_A$ receptors typically exist as a pentamer composed of two a subunits, two b subunits, and a g subunit (a2b2g), although considerable diversity exists. For example, substitution of the g subunit with a d subunit causes the receptor to be localized extrasynaptically, where it plays a larger role in the regulation of tonic neuronal activity. In addition, three r subunits have been cloned that do not appear to assemble with other subunits; instead, r subunits homo-oligomerize to form the $GABA_A$-r receptor (previously referred to as the $GABA_C$ receptor), which is highly expressed in the retina. This enormous receptor heterogeneity supports the complex, finely tuned role that inhibitory neurotransmission plays in brain function (Sigel and Steinmann 2012).

As a ligand-gated ion channel, the $GABA_A$ receptor requires two molecules of GABA to bind to the orthosteric site located at the interface between the a and b subunits. Ligand binding produces a conformational change leading to opening of the $Cl^{[?]}$ channel and neuronal inhibition driven via $Cl^{[?]}$-mediated hyperpolarization of the neuron. It should be noted that the pore permits bidirectional flow of $Cl^{[?]}$ ions, and the inhibitory effects of GABA are due to the $Cl^{[?]}$ concentration gradient, with high levels in the extracellular space relative to the cytoplasm. The $Cl^{[?]}$ concentration gradient is controlled and regulated by the K^+-$Cl^{[?]}$ co-transporter, KCC2, which maintains the intracellular $Cl^{[?]}$ concentration below its electrochemical equilibrium potential. KCC2 utilizes the K^+ gradient generated by the Na^+/K^+ ATPase to drive chloride from neurons. Interestingly, KCC2 expression is low during mammalian embryogenesis, a time when complex neural networks are forming and undergoing extensive remodeling (Rivera *et al.* 1999). By contrast, immature neurons express relatively high levels of NKCC1, a Na^+-K^+-$2Cl^{[?]}$ co-transporter that uses the electrochemical gradient of Na^+ (again, generated by the Na^+/K^+ ATPase) to transport Na^+, K^+, and $Cl^{[?]}$ into the cell. As long as NKCC1 transporters are expressed at sufficient levels, internal $Cl^{[?]}$ concentrations in neurons will be high, producing an outward driving force; therefore, $GABA_A$ channel opening causes $Cl^{[?]}$ to leave the cell and the membrane to depolarize. Thus, GABA can be either excitatory or inhibitory, depending on the relative intracellular concentration of $Cl^{[?]}$, which is high during early neuronal development (due to high NKCC1 expression) and low in mature neurons (due to KCC2 expression) (Rivera *et al.* 1999).

Given the enormous heterogeneity of the $GABA_A$ receptor, it is perhaps not surprising that numerous sites exist for allosteric modulation. Indeed, endogenous neurosteroids, such as allopregnanolone (a metabolite of progesterone), are known allosteric modulators of the $GABA_A$ receptor. Allopregnanolone (also known as brexanolone and marketed under the brand name Zulresso) was the first therapeutic to be approved by the FDA specifically for the treatment of postpartum depression. Furthermore, allopregnanolone is one of only two recently approved fast-acting antidepressants, with ketamine being the other (see "NMDA receptors" under "Ionotropic glutamate receptors" in the section "Glutamatergic Receptors"). Allopregnanolone readily crosses the blood-brain barrier and acts as a positive allosteric modulator at the $GABA_A$ receptor. Allosteric modulators act either as PAMs (which enhance Cl[?] currents through $GABA_A$ receptors to augment inhibitory signals) or as NAMs, or inverse agonists (which decrease Cl[?] flow through the pore of the receptor).

It is now well established that benzodiazepines, some of the most widely used psychotherapeutic drugs for the treatment of anxiety and sleep, function as PAMs by binding to an allosteric site on the $GABA_A$ receptor located at the interface between the a and g subunits (notably, g subunits are required for benzodiazepine binding and sensitivity). As PAMs, benzodiazepines increase the amplitude and frequency of inhibitory postsynaptic currents in response to GABA binding. It should be noted that $GABA_A$ receptors are widely distributed throughout the brain, and benzodiazepines target the majority of these synaptic receptors. For this reason, benzodiazepines are CNS depressants and produce side effects such as sedation, memory problems, and confusion.The extensive heterogeneity of $GABA_A$ receptors has prompted considerable research investigating whether the desirable and undesirable effects of benzodiazepines might be differentiated on the basis of the presence or absence of different subunit compositions (Olsen and Sieghart 2008). Given that the benzodiazepine binding site is located at the interface between the a and g subunits, and that there are six distinct a subunits, genetic knockouts have been used to examine the respective contributions of these subunits to the behavioral effects of benzodiazepines. Data from these genetic knockout studies indicate that a1-containing $GABA_A$ receptors mediate the sedative effects of benzodiazepines, whereas the a2-and/or a3-containing receptors mediate the anxiolytic effects (Atack 2005). For this reason, pharmaceutical companies have attempted to develop subunit-selective compounds capable of modulating a2/a3 but not a1 receptor function, in the hope that such compounds would be nonsedating anxiolytics. The investigational agent TPA-023 (MK-0777) was developed as a subunit-selective partial agonist at the a2 and a3 GABA_A receptor subunits. As predicted, it produced anxiolytic effects without sedative effects in animal models (Atack *et al.* 2006). In human trials, TPA-023 showed efficacy comparable to that of prototypic benzodiazepines but had fewer side effects (de Haas *et al.* 2007). Unfortunately, development of this compound for clinical use was discontinued because of toxic effects (cataracts); however, the premise of a2/a3-selective benzodiazepines for the treatment of anxiety appears promising.

Increased attention has been given to the relatively minor a5 subunit due to its enrichment throughout the hippocampus, where it accounts for approximately 20% of benzodiazepine binding sites. Thus, a5 subunit-selective PAMs and NAMs may be able to preferentially regulate hippocampal function following systemic administration. Clinical and preclinical research has identified augmented hippocampal activity as a key pathology contributing to schizophrenia (Lodge and Grace 2011). It is therefore possible that a5 subunit-selective PAMs may decrease aberrant hippocampal function and treat schizophrenia without producing the side effects associated with conventional D_2 receptor antagonist antipsychotics. Indeed, preclinical studies suggest that a5 subunit-selective PAMs are effective in reducing aberrant neurophysiological activity in models used to study schizophrenia (Gill *et al.* 2011). In addition, the hippocampus has been identified as a potential target for therapeutic intervention in depression, and novel a5 subunit-selective PAMs and NAMs have been developed that show antidepressant efficacy in rodent models (Carreno *et al.* 2017).

Metabotropic GABA receptors. The metabotropic GABA_B receptors are GPCRs assembled as heterodimers from two subunits of the receptor (GABA_{B1} and GABA_{B2}). Whereas GABA_A receptors mediate fast inhibitory signaling, activation of $GABA_B$ receptors produces a slower, more prolonged inhibition. These receptors not only are localized postsynaptically but also are found presynaptically on both GABA and glutamate neurons, where GABA spillover from local inhibitory synapses may readily activate $GABA_B$ receptors in a dynamic, state-dependent manner. Activation of $GABA_B$ receptors results in slow inhibitory postsynaptic potentials that are mediated by G protein-activated K^+ channels (Kir3 channels, or GIRKs) as well as inhibition of neurotransmitter release through inhibition of voltage-gated Ca^{2+} channels. In the classical pathway, $GABA_B$ receptor activation results in opening of the GIRK channel via direct interaction with the Gbg subunit of the heterotrimeric $G_{i/o}$ family (Figure 2-17). This GPCR-GIRK interaction mediates the inhibitory action of many neurotransmitters, including acetylcholine, dopamine, serotonin, and others. In addition, $GABA_B$ receptors are coupled to G_i and G_o and generally inhibit adenylyl cyclase activity. $GABA_B$ receptors are class C GPCRs (as are metabotropic glutamate receptors) and prototypical heterodimers. There are two subunits of the receptor, $GABA_{B1}$ and $GABA_{B2}$, that assemble as heterodimers by linking intracellular C termini. It is thought that the $GABA_{B1}$ subunit contains the orthosteric binding site, whereas the $GABA_{B2}$ subunit couples to the G protein. Therefore, it is necessary for $GABA_B$ receptors to form heterodimers for GABA-mediated signaling (Bettler *et al.* 2004).

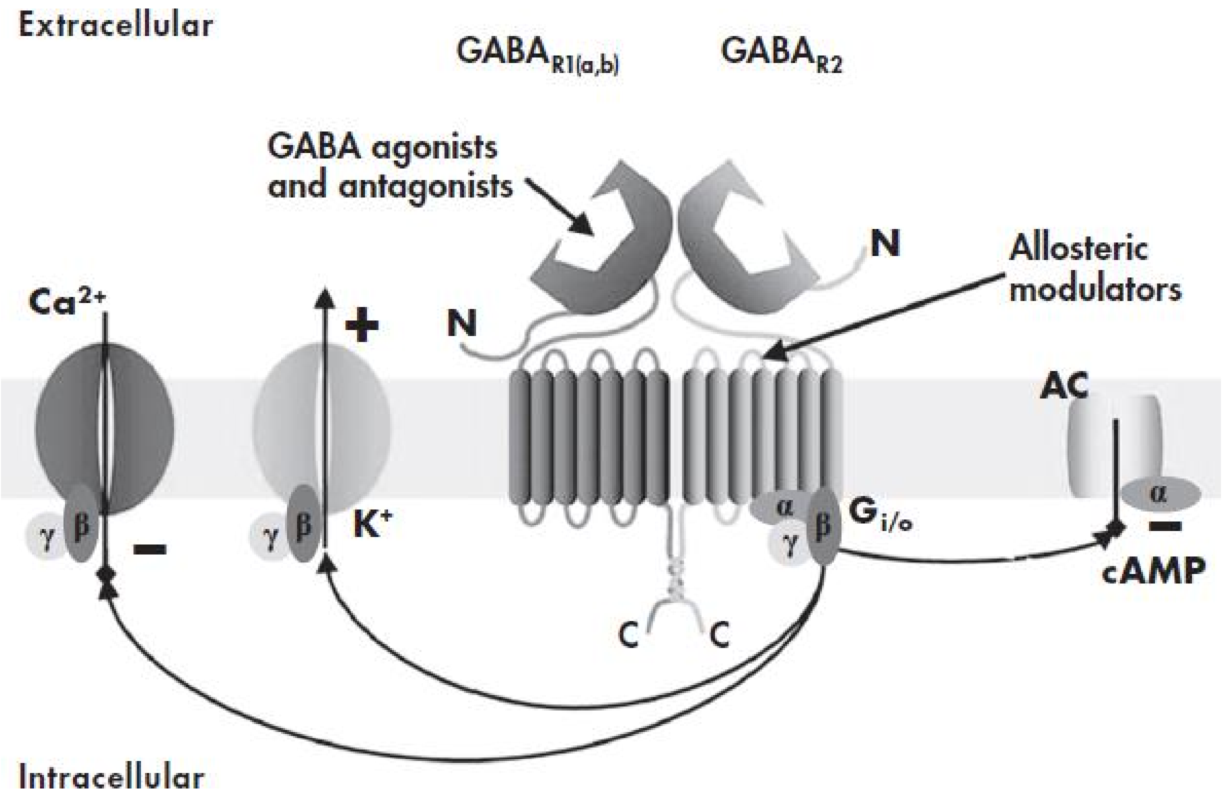


FIGURE 2-17. GABA$_B$ receptors.

See Plate 15 to view this figure in color.

The metabotropic GABA$_B$ receptors are GPCRs assembled as heterodimers from two subunits of the receptor (GABA$_{B1}$ and GABA$_{B2}$) coupled to G$_{i/o}$. Activation of GABA$_B$ receptors inhibits adenylyl cyclase, decreasing cAMP production. In addition, the Gbg subunit directly activates G protein-activated K^+ channels and inhibits voltage-gated Ca^{2+} channels, resulting in neuronal inhibition. AC = adenylyl cyclase; C = C-terminus; cAMP = cyclic adenosine monophosphate; GABA$_{R1(a,b)}$, GABA$_{R2}$ = GABA$_{B1}$ subunits; G$_{i/o}$ = Gi/o protein a subunit; N = N-terminus.

Source. Reprinted from Figure 1 (p. 756) in Filip M, Frankowska M: "Effects of GABA(B) Receptor Agents on Cocaine Priming, Discrete Contextual Cue and Food Induced Relapses." *European Journal of Pharmacology* 571(2-3):166-173, 2007 (https://doi.org/10.1016/j.ejphar.2007.05.069). Copyright (c) 2007, Elsevier B.V. Used with permission.

Baclofen, an analog of GABA first synthesized in the 1960s as a selective GABA$_B$ agonist, is the only FDA-approved selective GABA$_B$ receptor agonist. Sold under the brand name Lioresal, baclofen is used primarily in the treatment of spastic movement disorders associated with spinal cord injury or multiple sclerosis. Interestingly, baclofen analogs that block slow inhibitory signaling (i.e., GABA$_B$ antagonists) have been developed. Several of these GABA$_B$ receptor antagonists have been found to improve cognitive performance in a variety of animal models (Bowery 2006). Furthermore, when CGP36742, a selective brain-penetrant GABA$_B$ receptor antagonist, was investigated in a double-blind, placebo-controlled study, it appeared to be well tolerated and produced significant improvements in working memory, psychomotor speed, and attention in patients with mild cognitive impairment (Froestl *et al.* 2004). Whether GABA$_B$ receptor antagonists have clinical utility in treating cognitive impairment in patients with dementia remains to be evaluated fully.

GABA Transporters

Four subtypes of GABA transporters (GATs)--GAT1, GAT2, GAT3, and the betaine GAT (BGT1)--clear GABA from synapses and extracellular fluid. GAT1 and GAT3 are responsible for the majority of GABA clearance in the CNS. GAT1 is located in GABAergic axon terminals, astrocytes, oligodendrocytes, and microglia (Fattorini *et al.* 2020) and is densely expressed in the hippocampus and cerebellum, predominantly in the perisynaptic region of presynaptic boutons. However, GAT1 expression is more than threefold higher in astrocytic membranes than in axon terminals. GAT3 is located in brain stem and cortical neurons and is found predominantly on astrocytes (for a review, see Ryan *et al.* 2021). GATs belong to the SLC6 family. GAT1 is encoded by *SLC6A1* and GAT3 by *SLC6A11*. As is the case for other members of the SLC6 family, GATs use the concentration gradient of sodium (generated by the plasma membrane Na$^+$/K$^+$ ATPase) as the driving force to carry GABA across the plasma membrane into the cytosolic compartment. Once inside the cell, GABA is repackaged into vesicles by

VGAT. Like other members of the SLC6 family, GATs are tightly regulated by numerous endogenous and exogenous factors. Most studies of GABA transporters have focused on GAT1 and show that its uptake capacity and membrane expression are controlled by numerous kinases, phosphatases, SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein [SNAp] REceptors) complexes, growth factors, and auto-and heteroreceptors, as well as by GAT1 inhibitors. (For comprehensive reviews of GAT structure, function, and regulation, see Kristensen *et al.* 2011, Ryan *et al.* 2021, and Soudijn and van Wijngaarden 2000.)

Gene variants of GAT1, the majority of which are loss-of-function mutations, are associated with neurodevelopmental disorders such as intellectual developmental disorder (intellectual disability), autism spectrum disorder, and epilepsy (Bhat *et al.* 2021; Goodspeed *et al.* 2020), as well as with psychiatric disorders including anxiety disorders and schizophrenia (Rees *et al.* 2020; Thoeringer *et al.* 2009). GAT1 inhibitors, such as tiagabine, are used for treatment of epilepsy and have also been shown to be effective in the treatment of pain (Todorov *et al.* 2005; Zafar and Jabeen 2018). In clinical trials, tiagabine is being investigated for other indications, including as a treatment for cognitive deficits in schizophrenia (Xu and Wong 2018). Preclinical studies showed that tiagabine and other GAT1 inhibitors possess antinociceptve, antiallodynic, and anxiolytic properties, and these findings have encouraged further investigation of GAT1 inhibitors as therapeutics for a range of disorders (Ryan *et al.* 2021). Because of the prominent role of GAT1 (relative to other GATs) in CNS regulation of GABA uptake, development of non-GAT1 selective inhibitors has lagged behind development of selective GAT1 inhibitors. Consequently, less is understood about the therapeutic potential of GAT2, GAT3, and BGT1 (Sarup *et al.* 2003). It is known that GAT3 activity in astrocytes modulates excitatory neurotransmission in the hippocampus (Boddum *et al.* 2016). Accumulating pharmacological evidence indicates that GAT3, like GAT1, may be a promising target for treatment of numerous brain disorders (for reviews, see Damgaard *et al.* 2017 and Zareba *et al.* 2021).

Purinergic Transmission: Focus on Adenosine

The term *purinergic* was introduced by Burnstock in 1972 to describe transmission mediated by adenosine triphosphate (ATP), which is a purine by virtue of being a heterocyclic organic compound with two rings fused together (Burnstock 2014). As shown in Figure 2-1, adenosine (short for adenosine nucleoside) is also a purine. Adenosine is formed by the binding of adenine to D-ribose, making it a nucleoside. The original identification of adenosine was in 1929, when Drury and Szent-Gyorgyi extracted it from the mammalian heart (Drury and Szent-Gyorgyi 1929). It is now well established that adenosine has regulatory functions in organs such as the heart, kidney, lung, and gastrointestinal tract, and it is also known to play a role in respiratory and inflammatory diseases and in cancers (van Calker *et al.* 2019).

Our focus here, however, is on adenosine acting as a transmitter in the CNS. Adenosine is distributed widely in the brain. Even though adenosine does not meet all of the original criteria for a neurotransmitter mentioned at the beginning of this chapter, our expanding understanding of brain function validates its action as a neuromodulatory chemical that exerts both excitatory and inhibitory effects. Adenosine can be produced in three ways: 1) breakdown of ATP to adenosine diphosphate (ADP), followed by further breakdown to adenosine; 2) reaction of adenine with 1-phosphate ribose; and 3) hydrolysis of *S*-adenosyl-L-homocysteine to homocysteine and adenosine. Adenosine is released from both nerves and glia. Astrocytes are the main source of ATP released into synapses, from which it can be cleaved to adenosine (Boison 2010). Movement of adenosine across the plasma membrane is facilitated by bidirectional nucleoside transporters that either function passively or are active Na^+ transporters. Thus, the extracellular concentration of adenosine is regulated by its cellular release, its reuptake by transporters, and its conversion by enzymes on the cell surface (Effendi *et al.* 2020).

Purinergic receptors were first described in 1976. Two families of receptors were proposed: P_1 for adenosine and P_2 for ATP/ADP. The receptor for adenosine is now called the adenosine receptor, and there are four subtypes--A1, A2A, A2B, and A3--all of which have been cloned. The A1 and A2A receptors have higher affinity for adenosine than do either the A2B or the A3 receptor. Consequently, the A1 and A2A receptors are thought to be activated by normal physiological concentrations of adenosine, whereas the A2B and A3 receptors become activated when adenosine concentrations are elevated--as occurs, for example, in pathological conditions such as hypoxia (Burnstock 2014; Effendi *et al.* 2020). These four subtypes differ in their ligand-binding affinities, signaling mechanisms, and distribution in the brain. All four subtypes are GPCRs, with A1 and A3 receptors linked to G_i (so as to inhibit adenylyl cyclase) and A2A and A2B receptors linked to G_s (so as to stimulate adenylyl cyclase). A2B receptors stimulate not just adenylyl cyclase but also PLC. A3 receptors also stimulate PLC even though they inhibit adenylyl cyclase. A2A receptors can additionally be coupled to G_{olf} and activate PKA (Effendi *et al.* 2020; Liu *et al.* 2019; Figure 2-18).

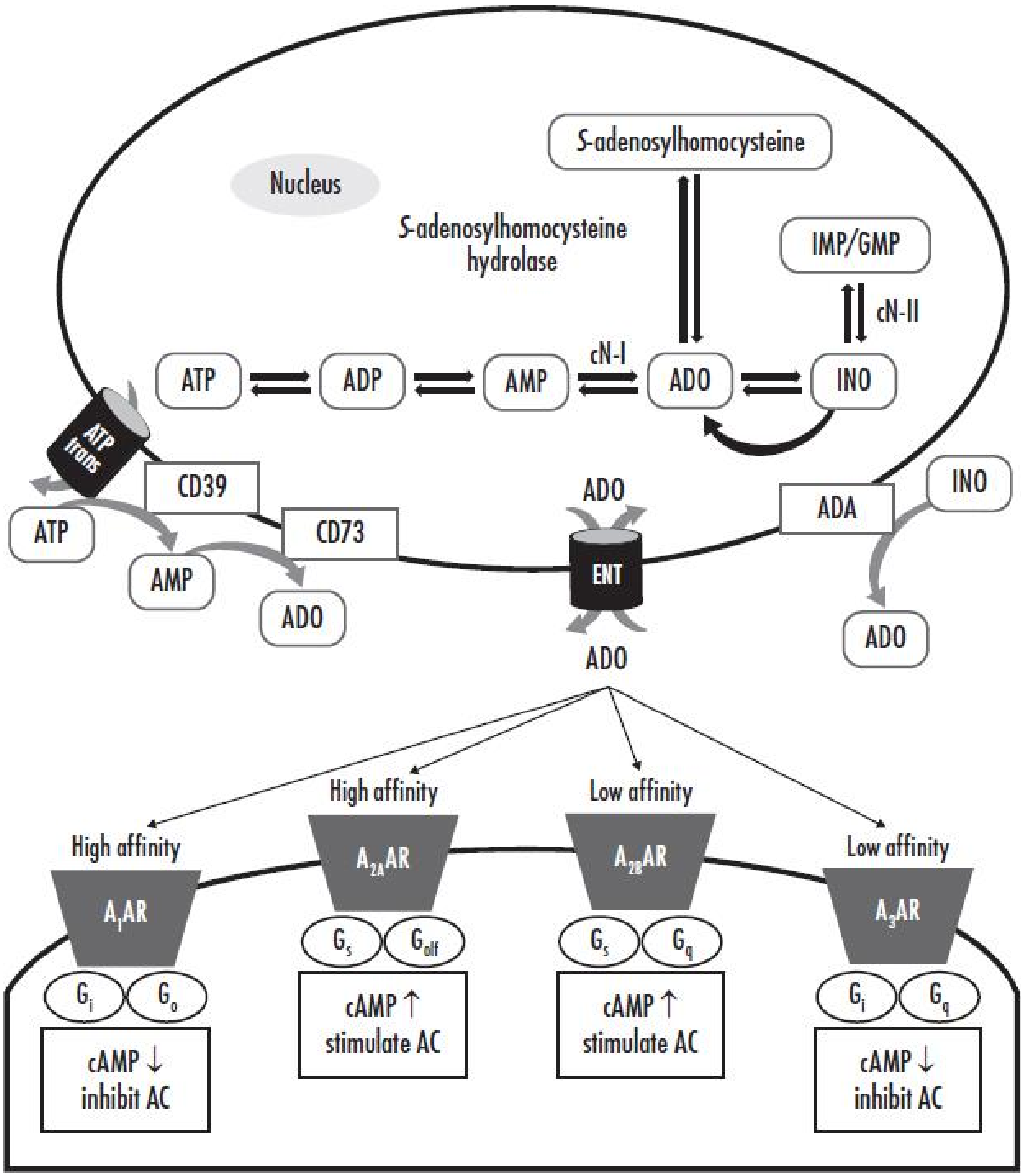

Nucleus
S-adenosylhomocysteine
S-adenosylhomocysteine hydrolase
IMP/GMP
cN-II
cN-I
ATP
ADP
AMP
ADO
INO
ATP trans
CD39
CD73
ATP
AMP
ADO
ADO
ENT
ADO
ADA
INO
ADO
High affinity
High affinity
Low affinity
Low affinity
A_1AR
A_{2A}AR
A_{2B}AR
A_3AR
G_i
G_o
G_s
G_{olf}
G_s
G_q
G_i
G_q
cAMP ↓ inhibit AC
cAMP ↑ stimulate AC
cAMP ↑ stimulate AC
cAMP ↓ inhibit AC

FIGURE 2-18. Production, transport, and metabolism of adenosine.

See Plate 16 to view this figure in color.

Intracellular adenosine is produced via dephosphorylation from the main source, AMP, via both cN-I and cN-II and hydrolysis of *S*-adenosyl-homocysteine through the enzyme *S*-adenosyl-L-homocysteine hydrolase. The extracellular formation of adenosine is the result of enzymatic cascades consisting of ATP transport, hydrolysis of ATP and ADP by CD39 to form AMP, and dephosphorylation of AMP by CD73. Extracellular adenosine binds adenosine receptors (A_1AR, A_{2A}AR, A_{2B}AR, and A_3AR) on the surface of cells. Each adenosine receptor is a GPCR that transmits the signal from adenosine by stimulating or inhibiting cyclic AMP (cAMP). AC = adenylyl cyclase; ADA = adenosine deaminase; ADO = adenosine; ADP = 5'-adenosine diphosphate; AMP = 5'-adenosine monophosphate; AR = adenosine receptor; ATP = 5'-adenosine triphosphate; CD = ectonucleotidase cluster of differentiation; cN = cytosolic 5'-nucleotidase; ENT = equilibrative nucleoside transporter; GMP = guanosine monophosphate; GPCR = G protein-coupled receptor; IMP = inosine monophosphate; INO = inosine.

Source. Reprinted from Figure 1 (p. 3) in Effendi WI, Nagano T, Kobayashi K, et al.: "Focusing on Adenosine Receptors as a Potential Targeted Therapy in Human Diseases." *Cells* 9(3):785, 2020 (https://doi.org/10.3390/cells9030785). Copyright (c) 2020 by the Authors. Licensee Multidisciplinary Digital Publishing Institute (MDPI), Basel, Switzerland. This article is an Open Access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

The A1 adenosine receptor has a widespread distribution in the brain and is found at its highest density in the cerebral cortex, thalamus, and lateral hypothalamus. The A2A receptor is found in brain areas rich in dopamine and is co-expressed with D_2 receptors on GABAergic striatopallidal neurons. The A2B receptor is found primarily in the CA_1 and CA_3 regions of the hippocampus. The A3 receptor is also widely distributed in the brain but is present at a much lower density than the A1 receptor (Liu *et al.* 2019).

Converging evidence indicates that adenosine plays a role in arousal and attention, given its hypnotic/sedative effects. Part of the evidence is the mild stimulant and alerting effects of methylxanthines, such as caffeine (coffee), theophylline (tea), and theobromine (cocoa), which are antagonists of A1 and A2A receptors. At higher doses, these substances can be anxiogenic and can even cause panic attacks, indicating a role for adenosine in anxiety (van Calker *et al.* 2019). Thus, agents selective for the various adenosine receptors may be useful in treating anxiety disorders. It has also been proposed that adenosine acts as a "retaliatory" substance to signal a disequilibrium between energy supply and demand so as to stimulate counterbalancing measures through activation of its various receptors (van Calker *et al.* 2019). Thus, for example, when production of ATP is reduced during hypoxia, adenosine accumulates and inhibits release of glutamate, which can be exocytotoxic.

Adenosine is the predominant presynaptic modulator of transmitter release in the brain. This occurs by its stimulation of presynaptic A1 receptors located on many different types of neurons (e.g., GABA, glutamate, dopamine, norepinephrine, 5-HT, ACh). Postsynaptic A1 receptors can inhibit signaling by causing hyperpolarization to reduce excitability. A2A receptors are present in both neurons and glia; in neurons, they are located on both presynaptic and postsynaptic neurons. Of current interest is the finding that A2A receptors can form heterodimers with other receptors, including the A1 receptor. Much attention has recently been focused on A2A/D_2 heterodimers. These heteromeric receptors have a pharmacology and function distinct from those of their constitutive receptors, and their possible role in schizophrenia and substance use disorders is an active area of research (Borroto-Escuela *et al.* 2020; Wydra *et al.* 2020). The A2A receptor itself may be involved in various effects of psychostimulants, nicotine, opioids, and ethanol, given that A2A receptor activation attenuates the rewarding effects of cocaine but not those of other psychostimulants. Such receptor stimulation also reduces opioid or alcohol withdrawal symptoms in laboratory animals (Wydra *et al.* 2020).

There is also an emerging literature examining the role of adenosine in depression and its treatment (Liu *et al.* 2019). For example, in rodents, antagonism of A2A receptors produces an antidepressant-like effect, whereas overexpression of these receptors causes depression-like behaviors, including anhedonia. By contrast, activation of A1 receptors produces an antidepressant-like effect (van Calker *et al.* 2019).

Peptidergic Neurotransmission

Neuromodulators encompass a variety of chemically different molecules that influence the activity and physiological and behavioral outcomes of classical neurotransmitters. Neuromodulators include adenine purines (e.g., ATP, nicotinamide adenine dinucleotide), endocannabinoids (e.g., 2-arachidonoylglycerol), neurotrophic factors (e.g., BDNF, fibroblast growth factor), gasotransmitters (e.g., nitric oxide, hydrogen sulfide), and neuropeptides. In this section we focus on general characteristics of peptidergic neuromodulators.

The idea that a peptide synthesized in neurons could be released and could act as a neurotransmitter was first introduced by the Dutch scientist David de Wied (De Wied and De Kloet 1987). Neuropeptide transmission differs from classical neurotransmission in several ways (Figure 2-19) (van den Pol 2012). Briefly, neuropeptides are synthesized as large precursor molecules (prepropeptides) in the cell body and dendrites, and the bioactive peptides are excised from the prepropeptides by convertase enzymes. After synthesis, neuropeptides are packed into large, dense-core storage vesicles (unlike the small vesicles in which nonpeptidergic neurotransmitters are stored) and are released by exocytosis from nerve terminals, dendrites, and soma. Release of neuropeptides generally is elicited by rapid-burst firing, prolonged depolarization, and elevated intracellular Ca^{2+}, and it often takes place in tandem with release of nonpeptidergic neurotransmitters (i.e., co-release). Unlike release of classical neurotransmitters, which occurs at the synaptic cleft of the active synapse, exocytosis of neuropeptides can occur at extrasynaptic sites along the neuronal membrane. Local diffusion ensures that signaling has a wide action range that includes the synaptic partner cell as well as both adjacent cells and remote sites (i.e., paracrine actions). Neuropeptides are not cleared by reuptake and recycling systems; instead, they are degraded by specific peptidases.

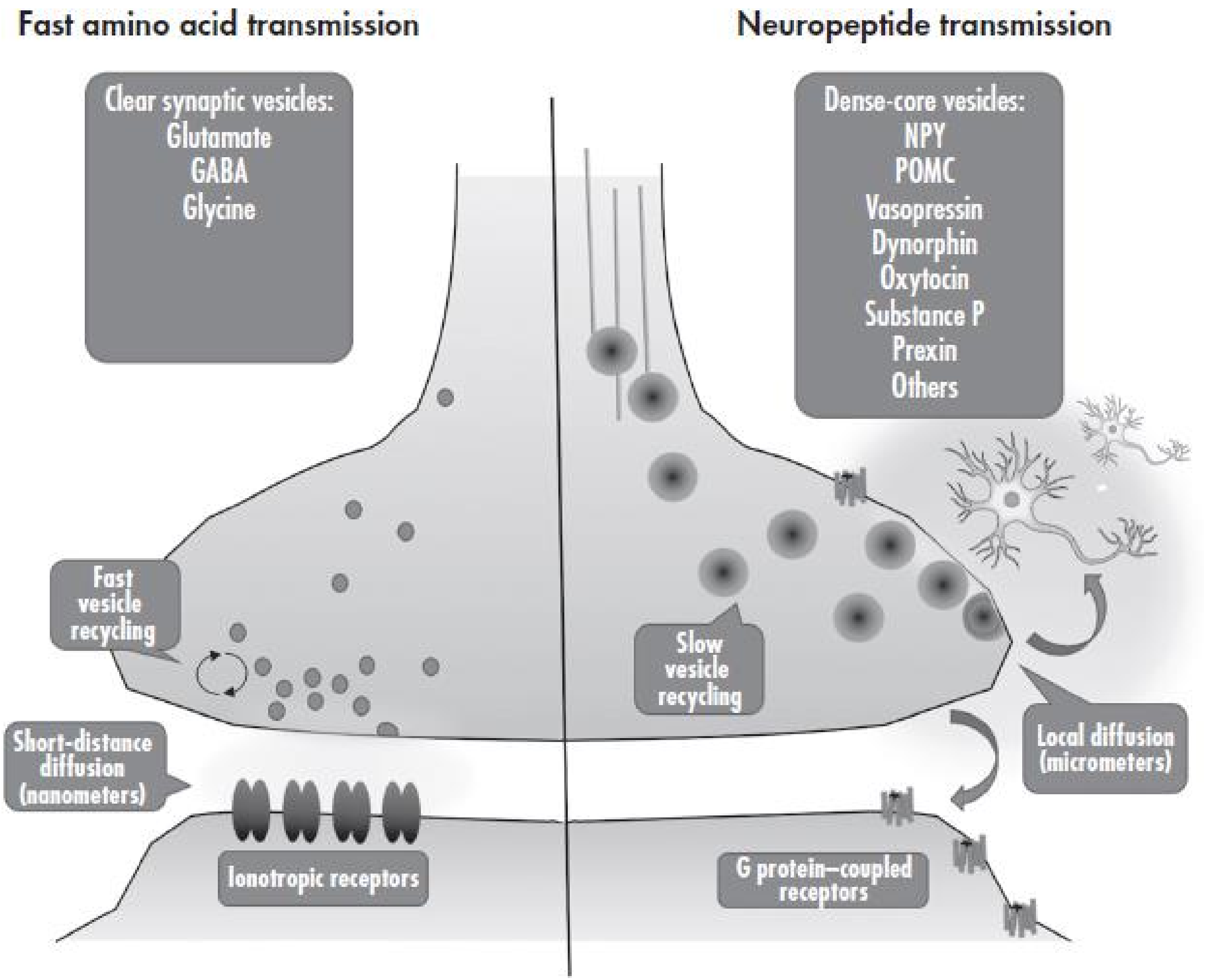

Fast amino acid transmission
Neuropeptide transmission
Clear synaptic vesicles:
Glutamate
GABA
Glycine
Dense-core vesicles:
NPY
POMC
Vasopressin
Dynorphin
Oxytocin
Substance P
Prexin
Others
Fast vesicle recycling
Slow vesicle recycling
Short-distance diffusion (nanometers)
Local diffusion (micrometers)
Ionotropic receptors
G protein–coupled receptors

FIGURE 2-19. Comparison of fast amino acid synaptic transmission *(left)* and slower neuropeptide transmission *(right)*.

See Plate 17 to view this figure in color.

NPY = neuropeptide Y; POMC = proopiomelanocortin.

Source. Adapted from Figure 3 (p. 103) in van den Pol AN: "Neuropeptide Transmission in Brain Circuits." *Neuron* 76(1):98-115, 2012 (https://doi.org/10.1016/j.neuron.2012.09.014). Copyright (c) 2012, Elsevier, Inc. Used with permission.

Most of the more than 100 different neuropeptides identified in the CNS act via one or more GPCRs. Hypothalamic neurons express large quantities of different neuropeptides (e.g., CRF, vasopressin, oxytocin, neuropeptide Y, somatostatin, leptin, ghrelin) that are important in regulating several homeostatic functions. However, neuropeptides are also present in other brain areas. For example, in the hippocampus, GABAergic interneurons have been shown to contain several neuropeptides, including neuropeptide Y, somatostatin, vasoactive intestinal polypeptide, cholecystokinin, dynorphin, enkephalin, neurokinin B, and substance P. Functionally, hippocampal neuropeptides may be involved in the regulation of neurotransmitter release (i.e., GABA and glutamate) at presynaptic terminals. Moreover, there is evidence that neuropeptides act as trophic factors for glial cells (van den Pol 2012).

Both preclinical and human postmortem studies show that dysregulation of neuropeptide signaling is associated with psychiatric conditions, but because of the different forms of receptors and associated signaling, identification of the specific effects of any one neuropeptide (or neurotransmitter) can be difficult. For example, galanin acting through receptors GalR1 and GalR3, which are GPCRs associated with G_i inhibitory

signaling, increases depressive-like behaviors, whereas galanin-dependent activation of GalR2 has anxiolytic effects and mediates resilience to stress (Hokfelt *et al.* 2018). Drugs targeting the galanin system, particularly GalR3 antagonists and GalR2 allosteric modulators, have been recently proposed as promising candidates for the treatment of depression and substance-related and addictive disorders (Genders *et al.* 2020; Hokfelt *et al.* 2018).

The role of brain gut peptides in mood disorders has also received considerable attention in recent years (Farzi *et al.* 2019; Lach *et al.* 2018; Rasmusson and Pineles 2018). Brain gut peptides (e.g., melatonin, ghrelin, substance P, cholecystokinin, neuropeptide Y) are involved in a number of homeostatic processes, including regulation of sleep, food intake, pain sensitivity, and inflammation. The neurobiology and pharmacology of this varied class of peptides is a current topic of intense research, as investigators and clinicians are acquiring a new appreciation of the impact of alterations in peripheral homeostasis in the etiology of psychiatric disorders.

In general, the role of neuropeptide systems in regulation of normal neurotransmitter function has been established in multiple preclinical studies, and therefore the idea of using these neuromodulators and their receptors as adjunctives to existing therapies has conceptually attracted increasing interest in recent years (Golyszny and Obuchowicz 2019). Space limitations prevent an extensive discussion of the neuropeptides known to exist in the mammalian brain; however, Table 2-5 highlights some of the major neuropeptides of potential psychiatric relevance. In the remainder of this section, we briefly discuss selected neuropeptide systems; for a more detailed discussion of neuropeptides as potential drug targets for psychiatric disorders, the interested reader is referred to recent comprehensive reviews of this emerging field of study (Abramova *et al.* 2020; Bali *et al.* 2014; Basu *et al.* 2021; Eiden *et al.* 2020; Gotter *et al.* 2012; Gupta and Prabhavalkar 2021).

TABLE 2-5. Selected peptides and their presumed relevance to psychiatric disorders and treatment

Group/peptide	Potential clinical relevance
Opioid and related peptides	
Endorphin	Analgesia for chronic pain
Enkephalin	Analgesia
Dynorphin	Analgesia
Nociceptin	Binds opioid-receptor-like 1 (ORL_1) receptor; increased pain perception
Gut-derived peptides	
Vasoactive intestinal peptide	Sexual behavior
Cholecystokinin	Anxiety/panic
Secretin	Anecdotal reports describing benefit in autism spectrum disorder and transient antipsychotic properties
Somatostatin	Mood disorders and treatment
Tachykinin peptides	

Group/peptide	Potential clinical relevance
Substance P (substance K)	Receptor is neurokinin-1 (NK_1); no efficacy shown for depression; inflammation
Neurotensin/neuromedin N	Analgesia, hypothermia; regulated by lithium; involved in dopamine signaling
Pituitary peptides	
Oxytocin	Affiliative, prosocial bonding behavior; decreases fear; may help increase sociability in autism spectrum disorder
Vasopressin	Also called antidiuretic hormone; receptors are V_{1A}, V_{1B}, and V_2; antagonists have anxiolytic, anti-aggression, and anti-irritability properties
Adrenocorticotropic hormone	Dysregulated in mood disorders
Melanocyte-stimulating hormone	Antidepressant and anti-anxiety properties
Hypothalamic-releasing factors	
Corticotropin-releasing factor	Anxiety and fear
Thyrotropin-releasing factor	Potential antidepressant effects
Others	
Calcitonin gene-related peptide	Regulated by electroconvulsive therapy and lithium
Angiotensin	Mood disorders, bipolar disorder
Leptin	Satiety signal; inhibits feeding drive
Cocaine-and amphetamine-related transcript	Substance use disorders, eating disorders

Group/peptide	**Potential clinical relevance**
Galanin	Potentially relevant for diagnosis of Alzheimer's disease and other neurocognitive disorders
Neuropeptide Y	Potential endogenous anxiolytic; regulated by antidepressants/lithium; reduced by early maternal separation; antagonists may decrease appetite
Orexin/hypocretin	Narcolepsy and other sleep abnormalities; eating disorders

Note. This table summarizes selected peptides and their presumed relevance for psychiatric disorders and their treatment; it is not meant to be an exhaustive listing of findings. It should also be noted that in some cases--for example, corticotropin-releasing factor (mood/anxiety), neuropeptide Y and neurotensin (regulation by medications), oxytocin (affiliative behavior), and orexin (narcolepsy)--data are quite convincing. In many other examples noted, the evidence must be considered preliminary but is promising and warrants further investigation. A discussion of these peptides is beyond the scope of this introductory chapter; nevertheless, readers are encouraged to explore the latest research in this rapidly evolving field.

Source. Reprinted from Table 2-3 (pp. 100-101) in Drazinic CM, Szabo ST, Gould TD, Manji HK: "Neurotransmitters and Receptors in Psychiatric Disorders," in *The American Psychiatric Association Textbook of Psychopharmacology*, 5th Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Association Publishing, 2017, pp. 45-116. Copyright (c) 2017, American Psychiatric Association. Used with permission.

Corticotropin-Releasing Factor

CRF is a 41-amino-acid neuropeptide (Vale *et al.* 1981) that mediates the response to stress by activating the hypothalamic-pituitary-adrenal (HPA) axis and by regulating neuronal activity in stress-responsive areas of the CNS. Following an acute stress experience (which may be real or perceived), CRF is released by parvocellular neurons of the paraventricular nucleus of the hypothalamus (PVN) into the median eminence and reaches the cells of the anterior pituitary through the microvasculature of the portal system. The binding of CRF to its receptor on the pituitary gland induces the synthesis and release of adrenocorticotropic hormone (ACTH) into peripheral blood circulation. ACTH reaches the adrenal gland and stimulates release of glucocorticoids that mediate several metabolic and neurophysiological effects of stress. Arginine vasopressin can be co-secreted with CRF during the stress response and contributes to the increase in ACTH levels (Itoi *et al.* 2004). Besides its role in the stress response, hypothalamic CRF is also responsible for circadian regulation of the HPA axis, with a peak in ACTH and glucocorticoid secretion at the onset of wakefulness and a trough 12 hours later. CRF is present in other brain regions within the CNS, notably within neurons of the locus coeruleus, the bed nucleus of the stria terminalis, and the dorsal raphe and amygdala, and it modulates the activity of these and other stress-responsive areas that express CRF receptors (Van Bockstaele and Valentino 2013; Young and Tong 2021).

CRF receptors are classified as CRF receptor type 1 and type 2 (CRFR1 and CRFR2) (Chen *et al.* 1993; Liaw *et al.* 1996). Both types of receptors are expressed in brain and peripheral tissue, with a higher prevalence of type 1 in the brain and of type 2 in the periphery. Other peptides that bind to these receptors with varying degree of affinity are urocortin-1 (Ucn-1), urocortin-2 (Ucn-2; also known as stresscopin-related peptide), and urocortin-3 (Ucn-3; also known as stresscopin) (Lewis *et al.* 2001; Reyes *et al.* 2001; Spina *et al.* 1996). CRFR1 and CRFR2 are both GPCRs that couple to G_s and activate cAMP-dependent PKA; however, evidence indicates that these receptors can also bind to G_q and $G_{i/o}$ in a tissue-specific manner. CRFR1s are highly expressed in the HPA axis and primarily mediate the activity of CRF neuropeptides under conditions of pronounced stress. Accordingly, CRF knockout mice and CRFR1 knockout mice show a severely reduced response of the HPA axis to stressful challenges (Smith *et al.* 1998). CRFR2 expression in the HPA axis is limited, but CRFR2 knockout mice still present an anxiogenic phenotype, with a rapid activation of the HPA axis and a lengthier recovery of the system after stress. This phenomenon might be explained by the fact that CRFR2s are highly expressed in neurons of the bed nucleus of the stria terminalis (BNST), which send inhibitory projections to the PVN, medial amygdala, and locus coeruleus and therefore normally inhibit HPA axis activity. Indeed, optogenetic activation of CRFR2 neurons in the BNST was found to reduce anxiety and to attenuate the neuroendocrine stress response (Henckens *et al.* 2017).

CRF is a well-known mediator of the pathophysiology of anxiety and depression. Numerous studies have reported a substantial link between depression and alterations in HPA axis activity (Keller *et al.* 2017); for example, increased levels of CRF in the cerebrospinal fluid, increased cerebrocortical CRF immunoreactivity, decreased CRFR1 binding, and decreased CRFR1 mRNA expression have been reported in postmortem

brain tissue of individuals who died from suicide (Sanders and Nemeroff 2016). Also, it has long been established that about 30%-50% of depressed patients demonstrate hypothalamic-pituitary-adrenocortical (HYPAC) hyperactivity, as revealed by resistance to the normal reduction in plasma 11-hydroxycorticosteroid produced by administration of the synthetic glucocorticoid dexamethasone (Carroll *et al.* 1968; Kocsis *et al.* 1985). Conversely, CRF hypoactivity has also been associated with certain subtypes of depression--namely, atypical and melancholic depression (Gold and Chrousos 2013; Kumsta *et al.* 2019). Given strong preclinical and clinical findings supporting the involvement of the CRF/CRFR system in anxiety and depression, a number of clinical trials using various CRFR1 antagonists were initiated; however, none produced satisfactory outcomes, either because of ineffectiveness or because of toxicity issues. Moving forward, it will be important to obtain a better understanding of the nuances of the CRF receptor family to allow development of molecules with a favorable safety profile that more reliably discriminate between CRFR1 and CRFR2. Additionally, therapeutic effectiveness may benefit from novel genetic and biochemical biomarkers capable of identifying individuals with a dysregulated CRF/CRFR system, for whom CRFR1 antagonists may be more effective as antidepressants or anxiolytics (Deussing and Chen 2018).

Oxytocin and Vasopressin

Oxytocin and arginine vasopressin (AVP) are two other neuropeptides gaining interest with respect to their relevance for psychiatric illnesses. These hormones have highly similar nine-amino-acid peptide sequences that differ by only two amino acids. Oxytocin signals through a GPCR (oxytocin receptor) that can bind to different G protein subtypes (G_q, G_i, G_o), depending on the concentration of the oxytocin ligand. AVP can bind to and modulate three types of vasopressin receptors: V_{1A}, V_{1B}, and V_2. V_{1A} and V_{1B} receptors are expressed in the CNS, especially in the olfactory bulb, anterior pituitary, cortex, hypothalamus, and hippocampus, and are coupled to $G_{q/11}$ proteins. V_2 receptors, largely present in the kidney, activate adenylate cyclase through G_s proteins.

Oxytocin and AVP are synthesized in magnocellular neurons of the PVN and the supraoptic nucleus of the hypothalamus. These neurons project their axons to the posterior pituitary gland (i.e., the neurohypophysis); from here, oxytocin and vasopressin vesicles are secreted directly into systemic circulation. As mentioned earlier, vasopressin can also be co-secreted with CRF. In the periphery, these hormones have important roles in the reproductive system during and after childbirth (oxytocin) and in the control of water reabsorption (AVP). In the brain, oxytocin and AVP act as neuromodulators of other neurotransmitter systems (e.g., the GABA and glutamate receptor systems [Bakos *et al.* 2018; Mitre *et al.* 2018]), and conversely, different neurotransmitters can regulate release of oxytocin and AVP and of other neuropeptides (Golyszny and Obuchowicz 2019).

The involvement of oxytocin and AVP in regulating emotions and social behaviors (parental, affiliative, and sexual behaviors for oxytocin; fear, aggression, and anxiety for AVP) is well established. For example, AVP has been shown to modulate aggressive behaviors and plasticity in the hippocampus through the V_{1B} receptors (Pagani *et al.* 2015). In a well-designed study, release of oxytocin within the amygdala was shown to be necessary and sufficient for modulation of fear memory and, with manipulation, to produce anxiolytic effects in mice (Hasan *et al.* 2019).

In addition to the role of oxytocin and AVP in modulation of emotional responses, a growing body of evidence points to the involvement of oxytocin and AVP signaling in cognitive functions, as well as in the etiology of neuropsychiatric disorders such as depression, bipolar disorder, autism spectrum disorder, schizophrenia, and borderline personality disorder (for a comprehensive review of this emerging field, see Abramova *et al.* 2020). Administration of oxytocin peptide intranasally has been adopted in clinical research and in therapeutic settings, following evidence that exogenous neuropeptides can cross the blood-brain barrier in small but functionally significant amounts via the receptor for advanced glycation end products (RAGE) (Yamamoto and Higashida 2020). Intranasal administration of oxytocin improved cognitive deficits and negative symptoms in individuals with schizophrenia (Ota *et al.* 2018), and it also improved social deficits and emotional dysregulation in individuals with autism spectrum disorder (Quintana *et al.* 2017). Study findings on the effects of intranasal oxytocin in depression have been mixed (MacDonald *et al.* 2013; Wong *et al.* 2021a). Improvements in social interaction in depressed patients were observed; however, in a subset of subjects with high introversion and a general tendency to self-isolate, oxytocin had anxiogenic effects, increased the bias to assign a negative valence to recalled events, and increased anhedonia). Thus, it appears that in depressed individuals, oxytocin may produce heterogeneous subjective effects that are sensitive to emotional context, individual personality traits, and attachment patterns (MacDonald *et al.* 2013; Wong *et al.* 2021a). Nevertheless, some evidence exists to suggest that intranasal oxytocin can be effective as an adjunct to SSRIs in improving symptoms in patients with treatment-resistant depression (Scantamburlo *et al.* 2015).

Although only a few reports have documented the use of modulators of the vasopressin system as therapeutics for mental disorders, some emerging studies indicate that this treatment is a viable option. As has been found for oxytocin, intranasal AVP has also been reported to have therapeutic potential in schizophrenia and in autism spectrum disorder (Geng *et al.* 2017; Parker *et al.* 2019). AVP can activate the HPA axis by stimulating AVP V_{1B} receptors located on the pituitary gland. Therefore, antagonists of V_{1B} receptors have been developed as potential antidepressants. In preclinical studies, direct antagonism of V_{1B} receptors successfully reduced stress-induced HPA axis activation and memory impairment (Barsegyan *et al.* 2015). Some of these antidepressant effects were reproduced in clinical trials, sparking hope for a potential use for V_{1B} receptor antagonists in depression therapy (Chaki 2021).

In conclusion, peptidergic neuromodulators are currently the focus of intense investigation for their potential use as standalone or adjunctive therapeutics for psychiatric disorders. Existing challenges to overcome include 1) the need to obtain a better understanding of peptide receptor pharmacology to help develop ligands and dosage regimens that differentiate between receptor systems in the CNS that regulate behavioral adaptation and those in the periphery that regulate homeostatic systems and 2) the need to develop more personalized approaches to therapy.

Opioids

Opioids, a class of drugs that act on opioid receptors, are commonly used for the treatment of moderate to severe acute, chronic, and inflammatory pain. The term *opiate* is often used interchangeably with *opioid*, and although all opiates are opioids, not all opioids are opiates. The term *opiate* refers to a drug that is derived from naturally occurring opium alkaloid compounds found in the opium poppy plant, whereas the term *opioid* encompasses any substance, whether natural, synthetic, or partially synthetic, that binds to opioid receptors.

The *naturally occurring opioids* are derived from the opium poppy plant (*Papaver somniferum*) and include opium, codeine, thebaine, and morphine. Historically (since ~ 3400 B.C.), opium was used to relieve pain, provide anesthesia, and induce sleep and was also used recreationally. Morphine, the primary active component of opium, continues to be the gold standard for treatment of pain to which all opioid analgesic drugs are compared. *Synthetic opioids* are compounds synthesized in a laboratory setting that have structures similar to those of naturally occurring opioids. Examples of synthetic opioids are fentanyl, methadone, carfentanil, and tramadol. Synthetic opioids have significant advantages over naturally derived opioids, including the capability for faster production (e.g., no time needed for plant cultivation) and lower costs. However, synthetic opioids and naturally occurring opioids have similar risks, including overdose and addiction. *Endogenous opioids*, discovered in the 1970s, are peptides that result from the proteolytic cleavage of precursor proteins, leading to the generation of more than 20 peptides. Cleavage of the precursor proteins prodynorphin, proenkephalin, proopiomelanocortin, and prepronociceptin produces dynorphins, enkephalins, endorphins, and nociceptin, respectively.

Both endogenous opioids and their opioid receptors are widely distributed throughout the central and peripheral nervous systems, particularly in regions that regulate pain, emotion, reward, stress responses, motivation, drug addiction, and autonomic control. The differential expression and location of endogenous opioids and their receptor subtypes likely account for the wide range of opioid-mediated effects.

Opioid receptors. ***Opioid receptor family and nomenclature*.** Opioid receptors are members of the large, seven-transmembrane-spanning GPCR family. There are three classical opioid receptors: mu (named after morphine), delta (named for the tissue--vas deferens--in which it was first identified), and kappa (named after the first ligand, ketocyclazocine, found to selectively activate the receptor). The approved opioid receptor nomenclature (as established by the Nomenclature Committee of the IUPHAR [NC-IUPHAR]) is summarized in Table 2-6. As defined by NC-IUPHAR, receptor classification is based on the endogenous ligands. For opioid receptors, the endogenous ligands are opioid peptides; thus, the receptors are designated as opioid peptide (OP) receptors. NC-IUPHAR has approved the use of Greek symbols for the three receptors--m, d, and k. These symbols can either stand alone or be abbreviated as mOP (or MOP, for mu), dOP (or DOP, for delta), and kOP (or KOP, for kappa). In addition to the three classical OP receptor subtypes, a fourth receptor subtype was identified that has close structural homology with and functional similarity to the OP receptors. This receptor--known as the opioid-receptor-like 1 (ORL_1) receptor, or the nociceptin opioid (NOP) receptor--is selectively activated by the endogenous ligand nociceptin/orphanin FQ (N/OFQ), which is derived from the precursor protein prepronociceptin. Although opioid ligands generally do not bind with high affinity to NOP receptors (an exception is buprenorphine [Toll *et al.* 2016]), the ORL_1 receptor is included as a nonopioid subcategory of the OP receptor family (Cox *et al.* 2015).

TABLE 2-6. Nomenclature, endogenous ligands, and major physiological effects of opioid receptors

Receptor subtype and abbreviations[a]	Endogenous ligands[b]	Physiological effects
mu, m, mOP, MOP, MOR[c]	b-Endorphin	Analgesia
	Enkephalins	Constipation
	Endomorphin-1	Euphoria
	Endomorphin-2	Dependence
		Respiratory depression
delta, d, dOP, DOP, DOR[c]	Enkephalins	Analgesia
	b-Endorphin	Anxiolysis
		Antidepressant

[a] Approved by the Nomenclature Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR).

[b] Although not selective among opioid receptors (e.g., enkephalins for mu and delta receptors), endogenous opioids have very low affinity for nonopioid receptors. The IUPHAR database defining the opioid receptor systems (with references to the most appropriate experimental models and selective radioligands, agonists, and antagonists) can be found at https://www.guidetopharmacology.org/.

[c] Although not recognized by NC-IUPHAR, the abbreviations MOR, DOR, and KOR (for mu opioid receptor, delta opioid receptor, and kappa opioid receptor, respectively) are still commonly used.

Source. Cox *et al.* 2015; Gendron *et al.* 2016; Toll *et al.* 2016; Wang 2019.

Receptor subtype and abbreviations[a]	**Endogenous ligands**[b]	**Physiological effects**
kappa, k, kOP, KOP, KOR[c]	Dynorphin A	Analgesia
	Dynorphin B	Dysphoria
	a-Neoendorphin	Diuresis
nociceptin, NOP	Nociceptin/orphanin FQ	Analgesia
		Anxiolysis
		Anti-reward

[a] Approved by the Nomenclature Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR).

[b] Although not selective among opioid receptors (e.g., enkephalins for mu and delta receptors), endogenous opioids have very low affinity for nonopioid receptors. The IUPHAR database defining the opioid receptor systems (with references to the most appropriate experimental models and selective radioligands, agonists, and antagonists) can be found at https://www.guidetopharmacology.org/.

[c] Although not recognized by NC-IUPHAR, the abbreviations MOR, DOR, and KOR (for mu opioid receptor, delta opioid receptor, and kappa opioid receptor, respectively) are still commonly used.

Source. Cox *et al.* 2015; Gendron *et al.* 2016; Toll *et al.* 2016; Wang 2019.

Opioid receptor heteromers. Substantial evidence supports the existence of functional and dynamic GPCR homomers and heteromers. All three classical opioid receptors have been shown to form heteromeric complexes with each other as well as with other classes of GPCRs. Although there is only one gene for each opioid receptor subtype, each receptor has been found to have more than one pharmacological subtype (e.g., dOP_1 and dOP_2 receptors; $kOP_{1\text{-}3}$ receptors). Receptor heteromers can have pharmacological properties--for example, ligand affinity, interprotomer allosterism, cellular signaling specificity, regulation--that are distinct from those of the individual receptors (Massotte 2015). It has been suggested that the propensity of

GPCRs to form opioid receptor heteromers (e.g., DOP-MOP, DOP-KOP) may explain the pharmacological subtypes of opioid receptors.

***Opioid receptor signaling*.** Opioid receptor activation leads to increased activity of a number of signal transduction pathways in cells of both the CNS and the periphery. The canonical signaling of opioid receptors is G_i protein mediated, leading to activation of three major inhibitory pathways known to reduce neuronal activity: 1) inhibition of adenylyl cyclase activity, 2) opening of GIRK ion channels, and 3) closing of voltage-gated calcium channels (Figure 2-20). In addition to coupling to G_i proteins, opioid receptors can signal via other G proteins as well as elicit non-G protein-mediated signaling to different intracellular signaling pathways. Furthermore, numerous mechanisms have been described whereby opioids can regulate receptor signaling, including phosphorylation, desensitization, and internalization. Phosphorylation of an opioid receptor can elicit b-arrestin recruitment to the receptor, which in turn elicits desensitization and internalization of the receptor. In addition, opioid receptor activation can lead to increased activity of the mitogen-activated protein kinases: ERK1/2, JNK, and p38. Opioid receptor activation has also been shown to elicit changes in the activity of transcription factors (e.g., cAMP response element-binding protein, DeltaFosB).

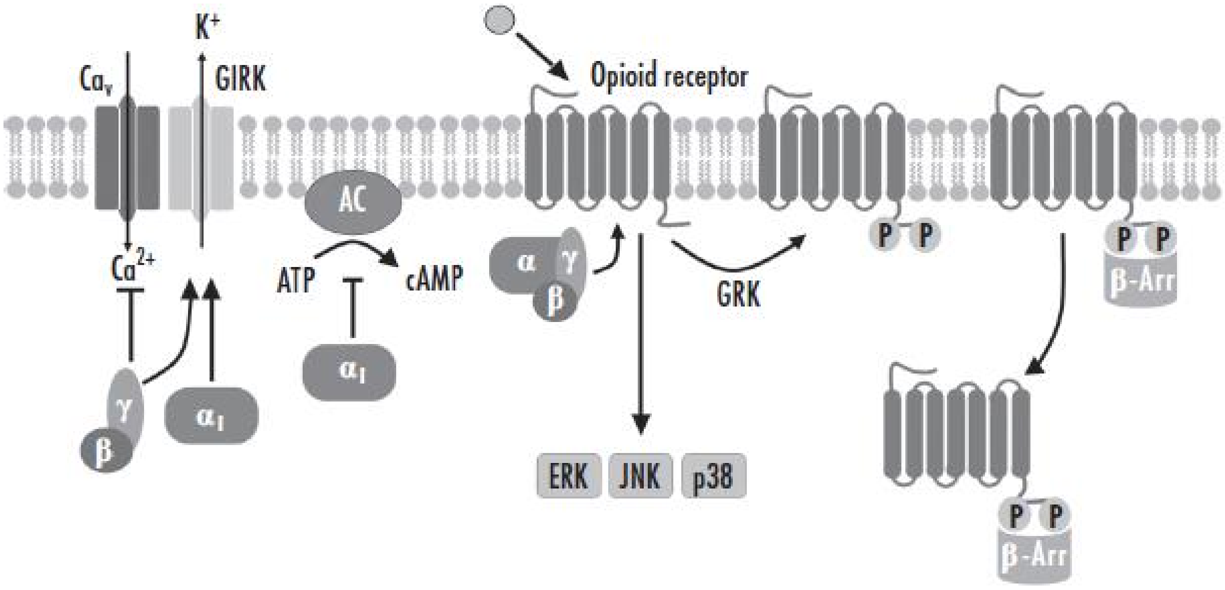


FIGURE 2-20. Opioid receptor-mediated signaling.

See Plate 18 to view this figure in color.

AC = adenylyl cyclase; a_i = G protein a i subunit; b-Arr = b-arrestins; ATP = 5'-adenosine triphosphate; Ca^{2+} = calcium ions; cAMP = cyclic adenosine monophosphate; Ca_v = voltage-gated calcium ion channel; ERK = extracellular signal-regulated kinase; GIRK = G protein-coupled inwardly rectifying potassium [channel]; GRK = G protein receptor kinase; K^+ = potassium ions; JNK = c-Jun N-terminal kinase; P = phosphorus; p38 = p38 mitogen-activated protein kinase (MAPK). a and bg refer to the respective heterotrimeric G protein subunits. See section "G Protein-Coupled Receptors" for details.

Biased signaling of opioids. Although effective as pain therapeutics for moderate to severe pain, opioid agonists are associated with serious adverse effects, including respiratory depression (which can lead to death), overdose, and substance use disorders. Efforts to develop opioid agonists that provide the same levels of analgesia without producing as many adverse effects have been based on the notion that a bias toward G_i protein activation and against b-arrestin recruitment would provide for more effective analgesia without producing adverse effects such as respiratory depression and constipation (Figure 2-21). Indeed, preclinical studies examining m opioid receptor agonists that are biased toward G_i proteins and away from arrestins have shown that these agents produce enhanced analgesia (Cunningham *et al.* 2019; Pineyro and Nagi 2021). However, other studies indicate that such biased agonists still produce respiratory depression and constipation (Gillis *et al.* 2020), suggesting that these m opioid receptor-mediated adverse effects are elicited--at least in part--by activation of other signaling molecules (i.e., other than b-arrestins and perhaps including G_i proteins).

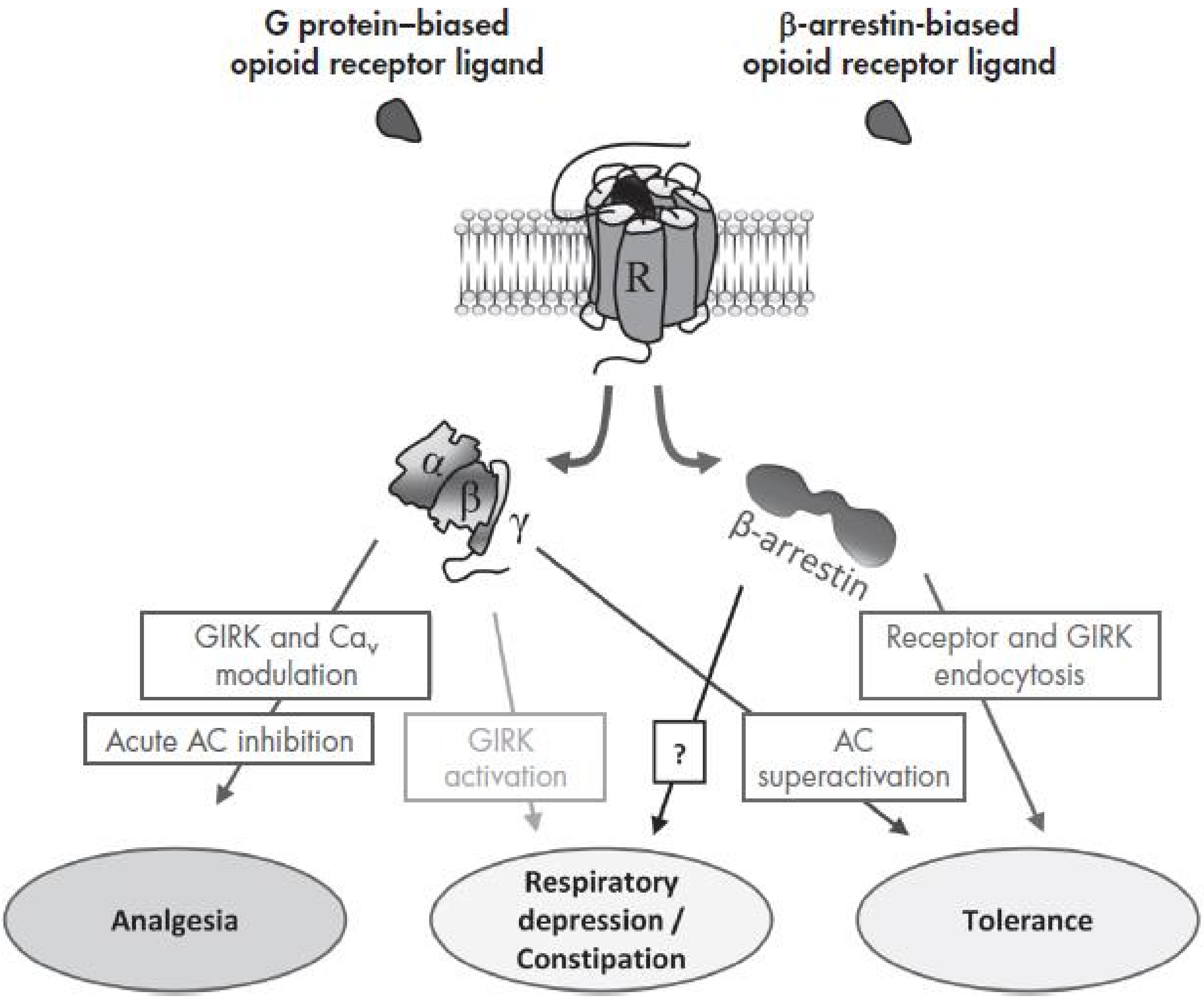

G protein–biased opioid receptor ligand
β-arrestin-biased opioid receptor ligand
R
α
β
γ
β-arrestin
GIRK and Ca_v modulation
Acute AC inhibition
GIRK activation
?
AC superactivation
Receptor and GIRK endocytosis
Analgesia
Respiratory depression / Constipation
Tolerance

FIGURE 2-21. Signaling bias of opioid ligands.

See Plate 19 to view this figure in color.

Opioid receptor activation of G protein signaling leading to increased ion channel activity (GIRK and Ca_v channels) and inhibition of AC was thought to mediate analgesia, whereas b-arrestin signaling was associated with adverse side effects (e.g., constipation, respiratory depression). However, more recent studies suggest that b-arrestin signaling may not underlie the development of constipation and respiratory depression, whereas G protein-mediated pathways may contribute to the development of these adverse effects. AC = adenylyl cyclase; Ca_v = voltage-gated calcium channel; GIRK = G protein-coupled inwardly rectifying potassium [channel].

Source. Reprinted from Figure 1 (p. 2) in Pineyro G, Nagi K: "Signaling Diversity of Mu-and Delta-Opioid Receptor Ligands: Re-Evaluating the Benefits of b-Arrestin/G Protein Signaling Bias." *Cellular Signalling* 80:109906, 2021 (https://doi.org/10.1016/j.cellsig.2020.109906). Licensed under a Creative Commons Attribution 4.0 license; https://creativecommons.org/licenses/by/4.0.

Allosterism and opioid receptors. An allosteric ligand binds to a site on a receptor that is topographically distinct from the orthosteric ligand binding site; thus, both ligands can occupy the receptor at the same time. Consequently, an allosteric ligand can stabilize the receptor in a conformation for which the affinity and/or intrinsic efficacy of an orthosteric ligand can be different (enhanced or reduced). Importantly, the new receptor conformation stabilized by an allosteric ligand influences orthosteric ligand affinity and/or intrinsic efficacy in a ligand-dependent manner (Gentry *et al.* 2015; Kenakin 2021; Wenthur *et al.* 2014). This ligand dependence is also commonly referred to as *probe dependence*. Recently, in response to the opioid epidemic, the National Institute on Drug Abuse (NIDA) announced that identification of PAMs at the m opioid receptor is a medication priority (Rasmussen *et al.* 2019). Thus, current strategies in drug discovery are focused on identification of PAMs that can enhance the therapeutic effects of endogenous opioid peptides (preserving their temporal and spatial release patterns) and/or that can modulate the effects of opioids (e.g., fentanyl, morphine) such that analgesia is enhanced and adverse effects (e.g., respiratory depression) are minimized (Kandasamy *et al.* 2021; Pryce *et al.* 2021).

Opioid receptor expression in brain and physiological effects.

Clinically, opioids are used predominantly for treatment of pain. All opioid receptors can produce analgesic effects via activation of receptors expressed in brain regions involved in pain processing and perception as well as in the spinal cord and in the periphery. However, in addition to having specific brain region distributions, each receptor subtype can elicit physiological responses other than analgesia.

***Mu opioid receptors*.** Mu opioid receptors are expressed centrally at moderate to high densities in the cerebellum, nucleus accumbens, caudate nucleus, cerebral cortex, and amygdala. All opioids currently in clinical use for treatment of pain are m opioid receptor agonists. In addition, m opioid receptors are involved in reward processing of both natural stimuli and drugs of abuse, actions that promote recreational drug use and the onset of addictive behavior (for a review, see Lutz and Kieffer 2013). Importantly, the worldwide opioid epidemic is a result of abuse of opioids that target m opioid receptors. One of the approved treatments for opioid use disorder (which is considered a psychiatric illness [American Psychiatric Association 2013]) is methadone, a long-acting synthetic opioid agonist that has been used for nearly 50 years as a maintenance therapy to treat opioid use disorder. Furthermore, the long-acting ligand buprenorphine, which is a partial (weak) agonist at m receptors, an antagonist at k receptors, and a full agonist at NOP receptors, is also used to treat opioid use disorder (Cao *et al.* 2023; Watan Pal *et al.* 2021). The opioid antagonists naloxone (Narcan) and naltrexone (Vivitrol), respectively, are used to reverse severe respiratory depression following opioid overdose and to treat opioid and alcohol use disorders (Kranzler and Soyka 2018; Lee *et al.* 2018).

Delta opioid receptors. Delta opioid receptors are expressed in the cerebral cortex, amygdala, pontine nucleus, nucleus accumbens, and olfactory tubercle. d opioid receptor agonists have shown promise for treatment of chronic pain. However, in contrast to m receptor agonists, d opioid receptor agonists do not readily cause physical dependence, elicit respiratory depression, or produce rewarding effects. Although some older d opioid receptor agonists (e.g., SNC80) have been shown to induce mild epileptic seizures in rodents (Broom *et al.* 2002) and rhesus monkeys (Danielsson *et al.* 2006), second-generation d receptor agonists do not appear to produce these effects, perhaps due to biased signaling (Chung *et al.* 2015). Furthermore, studies suggest that d opioid receptor agonists can produce anxiolytic effects as well as promote positive affect (Valentino and Volkow 2018). Thus, there is increasing interest in the development of d opioid receptor agonists for the treatment of mood disorders such as depression and anxiety.

Kappa opioid receptors. Kappa opioid receptors are widely expressed in the CNS, including the mesolimbic system, hypothalamus, amygdala, and hypothalamic-pituitary-adrenal (HPA) axis. In contrast to m and d opioid receptor agonists, k opioid receptor agonists produce dysphoria and negative affects as well as psychotomimetic effects. Furthermore, dysregulation of the dynorphin/kappa opioid receptor (KOR) system has been shown to be involved in numerous psychiatric disorders, including depression and substance use disorders/addiction (Crowley and Kash 2015), as well as in both positive and negative symptoms of schizophrenia (Clark and Abi-Dargham 2019).

NOP receptors**.** NOP receptors are highly expressed in the ventral tegmental area, nucleus accumbens, and prefrontal cortex. Preclinical studies indicate that NOP receptor agonists are effective analgesics in primates, but not in rodents. However, NOP receptor agonists are neither rewarding nor aversive and can attenuate the rewarding effects of opioids as well as those of other drugs of abuse (Toll *et al.* 2016). In addition, activation of the NOP receptor via intracerebroventricular administration (or microinjection into the central amygdala) of its selective endogenous agonist nociceptin (N/OFQ) reduces anxiety-related behavior in rodents (Schroder *et al.* 2014). NOP receptor antagonists may have a role in treating depression (Redrobe *et al.* 2002). Although these agents are promising, much more work is needed to determine whether NOP receptors will be useful targets for therapeutics.

Conclusion

In this chapter we have provided an overview of neurotransmitters and their receptors in the brain that are relevant for psychiatric disorders and their treatment. We have emphasized signaling pathways for different neurotransmitters, novel signaling properties of drugs acting on receptors (e.g., biased agonism), the many types of specific receptors for neurotransmitters and their many different subunits, receptors existing as either homodimers or heterodimers, constitutive receptor activity, and the regional location of receptors and transporters. The reason for such detail is simple. The more the existence of such phenomena is recognized, the more targets become available for drug development that hopefully will offer advantages over existing drugs. In some cases, this knowledge has already borne fruit, but in other instances, preclinical data have not yet been translated into useful therapeutics in patients. Nevertheless, efforts are ongoing, and there is no doubt in the authors' minds that the next 10 years will lead to much-improved therapeutics based on such detailed knowledge of brain function.

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CHAPTER 3

Genetics and Epigenetics

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Genetics and genomics are among the most important tools in modern psychiatric research. Genomics in psychiatry has developed into a multidisciplinary assembly of huge data. In this chapter, we cover basic concepts as well as the latest methodologies and define key terms currently used in psychiatric genomics. An overview of the genetic methods available in psychiatric research today is illustrated in Figure 3-1. Our goal is to facilitate physicians' and scientists' interpretation of the avalanche of genetic and genomic data, including epigenetics, that are accumulating in psychiatry. The potential impact of this new information on improving diagnosis and treatment of these disorders is discussed. Throughout this chapter, terms in common use in the genetics and genomics literature are italicized on first use and are defined.

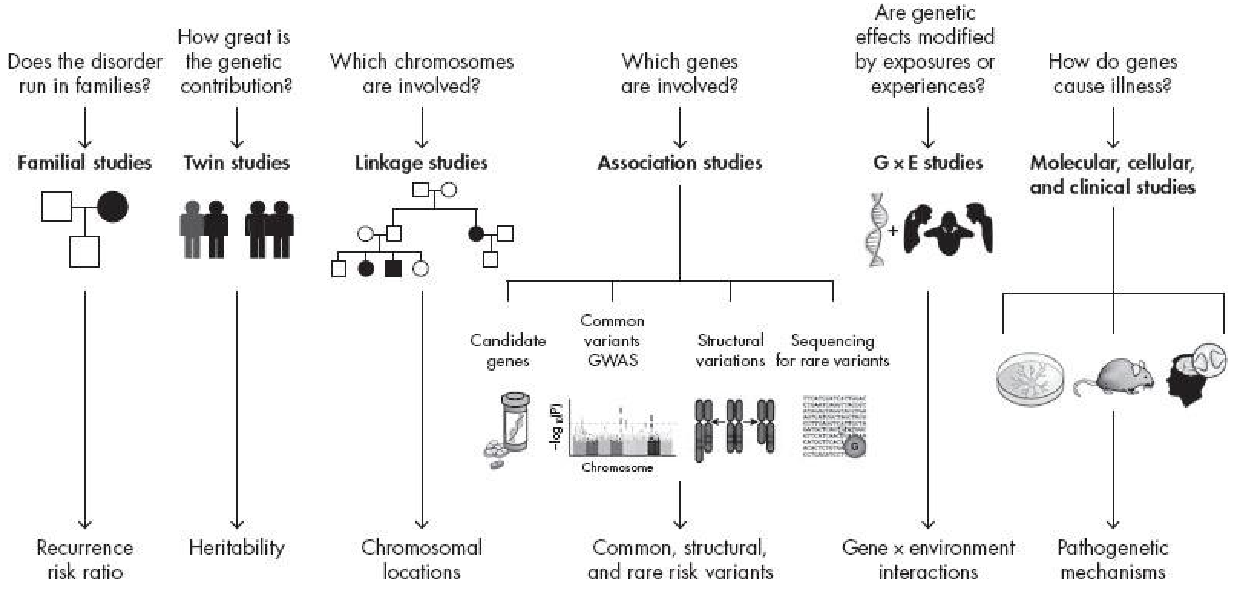
Does the disorder run in families?
How great is the genetic contribution?
Which chromosomes are involved?
Which genes are involved?
Are genetic effects modified by exposures or experiences?
How do genes cause illness?
Familial studies
Twin studies
Linkage studies
Association studies
G × E studies
Molecular, cellular, and clinical studies
Candidate genes
Common variants GWAS
Structural variations
Sequencing for rare variants
−log10(P)
Chromosome
Recurrence risk ratio
Heritability
Chromosomal locations
Common, structural, and rare risk variants
Gene × environment interactions
Pathogenetic mechanisms

FIGURE 3-1. Overview of genetic methods used in psychiatry research.

See Plate 20 to view this figure in color.

This figure summarizes the different steps from heritability to understanding pathomechanisms using genetic methods. G x E = gene x environment; GWAS = genome-wide association studies.

Source. Adapted from Figure 1 (p. 298) in Smoller JW: "The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders." *Neuropsychopharmacology* 41(1):297-319, 2016 (https://doi.org/10.1038/npp.2015.266). Copyright (c) 2016, American College of Neuropsychopharmacology.

Epidemiological Basis for Genetic Contributions to Neurobehavioral Disorders

Insights From Adoption and Twin Studies

Genetic epidemiological studies have established that most psychiatric disorders have a substantial genetic component. Genetic epidemiology uses family, adoption, and twin studies to assess the contribution of familial, environmental, and genetic factors to a trait of interest. A family study uses a *pedigree* (a type of family tree) to establish whether a given disorder "runs in the family"; however, these studies cannot easily distinguish whether such familiality is due to genetic or environmental factors. An everyday example of this distinction is the difference between the ability to acquire language (a genetic trait that distinguishes humans from other species) and the native language spoken by a given person (familial but entirely environmentally determined). Large registries of familial data, such as the Swedish National Register, have provided strong evidence for heritability of psychiatric disorders. Analysis of 3 million full and half-siblings showed that for most disorders, over 50% to up to 80% of the variance can be attributed to genetic factors, with strong evidence for a large proportion of shared genetic factors (Pettersson *et al.* 2016).

Adoption and twin studies differentiate between genetic and environmental influences on traits by accounting for each separately. Adoption studies investigate whether an individual's risk for a psychiatric disease depends on the mental health status of the biological or adoptive parents to disentangle genetic (i.e., similarity to biological parents, who had little or no interaction with the adoptee) from environmental (i.e., similarity to adoptive parents, who provided the environment) influence (Cadoret 1986; Tienari and Wynne 1994; Tienari *et al.* 2004). Practical, ethical, and legal obstacles make large-scale adoption studies difficult to conduct. Twin studies, while also challenging, are more tractable, and large twin registries are now available globally (Busjahn 2002).

In twin studies, the degree of correlation between twins for an investigated trait is compared for monozygotic (MZ; i.e., identical) and dizygotic (DZ; i.e., non-identical) twins to gain information on the amount of genetic and environmental influence on a certain trait (Figure 3-2). Although neither the pre-nor the postnatal environments of twins are exactly identical, for a first approximation, MZ and DZ twins are equally correlated for relevant environmental exposures (Kendler and Gardner 1998). The trait correlation between MZ and DZ twins therefore allows estimation of the degree to which the additive genetic, shared, or individual-specific environment contributes to the likelihood of a given trait.

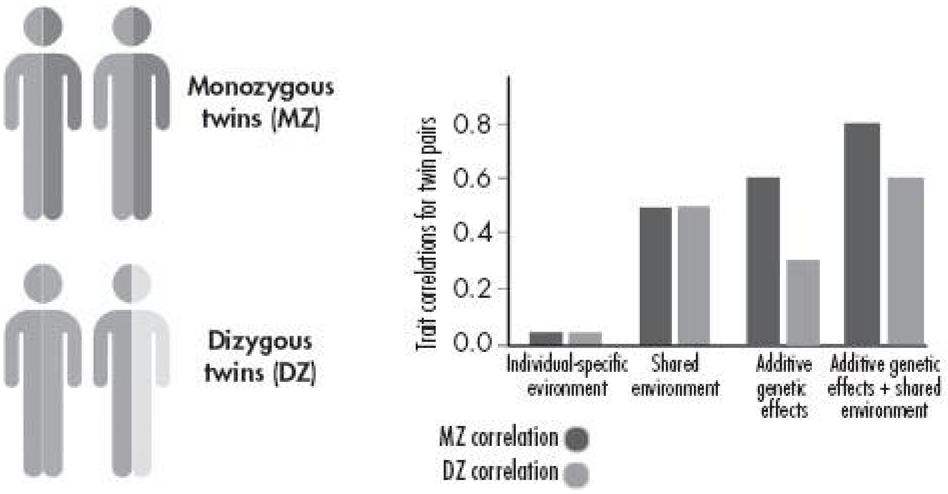

FIGURE 3-2. Patterns of intrapair correlations in twins and the source of variance implied.

See Plate 21 to view this figure in color.

Correlation of phenotypes/traits between monozygotic (MZ) and dizygotic (DZ) twin pairs illustrating different scenarios of genetic and environmental contributions to disease. Intrapair correlations of around zero imply effects of individual-specific environment. Equal intrapair correlations that are greater than zero for MZ and DZ twins imply effects of shared environment. Correlations for MZ twins that are twice as great as those for DZ twins imply additive genetic effects. Correlations for MZ twins that are greater than--but not twice as great as--those for DZ twins imply additive genetic effects and shared environment effects. Correlations of less than 1.0 are likely mediated by individual-specific environment effects.

Source. Created with BioRender.com.

In the largest conducted meta-analysis of twin studies (over 14.5 million twin pairs), an average 49% heritability was found for the 18,000 human traits examined. For most of the traits (two thirds), the correlation between MZ twins was double that seen for DZ twins, indicating a simple genetic model with independent effects of genes. Nevertheless, for the remaining third, the effects of genes cannot be independent (Polderman *et al.* 2015). The data are available through the MaTCH (Meta-Analysis of Twin Correlations and Heritability) resource (http://match.ctglab.nl/#/home). Twin studies have firmly established genetic contributions for all psychiatric disorders, with *heritability estimates* (the proportion of risk for a disorder attributable to the additive effects of genes) ranging from 30% to 80% for most common psychiatric disorders (Table 3-1). A discrepancy exists between heritability estimates from family studies and those from population cohorts, which are always lower. For example, heritability estimates for schizophrenia from twin studies averaged about 0.8 (Sullivan *et al.* 2003), whereas a Swedish population study estimated a heritability of 0.65 for schizophrenia and 0.59 for bipolar disorder (Lichtenstein *et al.* 2009). Using a population cohort of more than 2.6 million Danes, Wray and Gottesman (2012) estimated a heritability of 0.67 for schizophrenia, 0.32 for major depressive disorder (MDD), and 0.62 for bipolar disorder.

TABLE 3-1. Heritability scores for major psychiatric illnesses, with focus on results of meta-analyses

Disorder	Heritability	*N* in meta-analysis	References
Autism (DSM-5 autism spectrum disorder)	> 0.8	--	Bailey *et al.* 1995; Rutter 2000
Schizophrenia	0.81 (0.73-0.9)	12 studies (Sweden, United States, England, Norway, Denmark, Finland, Germany)	Sullivan *et al.* 2003 (meta-analysis)
Bipolar disorder	0.79-0.85	--	Kendler *et al.* 1995; McGuffin *et al.* 2003
Major depressive disorder	0.37 (0.31-0.42)	5 studies (United Kingdom, Sweden, United States) (*N* > 21,000)	Sullivan *et al.* 2000 (meta-analysis)

Disorder	Heritability	*N* in meta-analysis	References
Panic disorder	0.43 (0.32-0.53)	3 studies ($N >$ 9,000)	Hettema *et al.* 2001 (meta-analysis)
Generalized anxiety disorder	0.32 (0.24-0.39)	2 studies ($N >$ 12,000)	Hettema *et al.* 2001 (meta-analysis)
Specific phobia	0.25-0.35	--	Kendler *et al.* 1992, 2001
Social phobia (DSM-5 social anxiety disorder)	0.20-0.30	--	Hettema *et al.* 2001; Kendler *et al.* 1992
Agoraphobia	0.37-0.39	--	Kendler *et al.* 1992, 2001
OCD	0.45-0.65 (in children); 0.27-0.47 (in adults)	--	van Grootheest *et al.* 2005 (review)

Disorder	**Heritability**	***N* in meta-analysis**	**References**
Anorexia nervosa	0.56 (0.00-0.86)	Swedish twin registry ($N >$ 30,000)	Bulik *et al.* 2006
Bulimia nervosa	0.28-0.83	--	Bulik *et al.* 2000 (review)
Alcohol dependence (DSM-5 alcohol use disorder)	0.48-0.73 (men); 0.51-0.65 (women)	--	Tyndale 2003 (review)
Nicotine addiction (DSM-5 tobacco use disorder)	0.4-0.7	--	Li 2003; Tyndale 2003 (reviews)
Antisocial personality disorder	0.32	51 studies	Rhee and Waldman 2002 (meta-analysis)

Additionally, genetic epidemiology allows exploration of more complex questions, such as whether the same genetic risk factors are shared by different psychiatric disorders (cross-disorder risk) and between sexes and whether these genetic risk factors can moderate or be moderated by the effects of environmental risk factors (Kendler 2001). As

such, they can therefore shape follow-up molecular genetic studies. For example, a twin study suggested that genetic risk factors for MDD could in part act by increasing vulnerability to stressful life events (Kendler 1995). Genetic epidemiological studies have been an important foundation of psychiatric genetics and are likely to continue to contribute more elaborate disease models for future molecular genetic analysis. The major limitation of these studies, however, is that the estimated heritability of twin studies is only an estimate of the aggregate genetic effect. Heritability does not provide any information about which specific genes contribute to the risk for a disorder.

Using a novel method of approximating the genetic risk using extended pedigrees, Kendler *et al.* (2020, 2021) recently calculated family genetic risk scores (FGRS) for a number of psychiatric disorders using the Swedish national sample. The authors reported that all diagnostic groups had elevated FGRSs and found clear patterns across disorder groups and higher FGRS in individuals with earlier age at onset and higher recurrence. This work highlights the need to look beyond specific diagnoses of individuals, toward their genetic risk pattern for all disorders.

Human Genetic Variation

Genetic epidemiological studies can indicate the presence of an aggregate genetic effect but cannot identify which type of or how many variations contribute to the effect.

In this section, the glossary provides an overview of the types of genetic variation, followed by some examples illustrating the implications of each variation type in psychiatric disorders.

Glossary of Molecular Genomic Variation Terms

An *allele* is a variation in the DNA sequence that occurs at a particular polymorphic site on one chromosome. Every individual with a normal set of chromosomes has two alleles for each polymorphism on the *autosomes* (non-sex chromosomes, numbers 1-22). On the sex chromosomes, men have only one allele each for all polymorphisms located on the X and Y chromosomes, whereas women carry two copies of each X-linked allele.

A *genotype* is the combined description for the variation at a particular corresponding point on homologous chromosomes and is expressed as two alleles. When the alleles on both chromosomes are the same, it is a homozygous genotype. When the alleles differ, it is a heterozygous genotype.

A *haplotype*, a term derived from the abbreviation of *haploid genotype*, is the sequence of alleles along an adjacent series of polymorphic sites on a single chromosome that are inherited together due to strong linkage disequilibrium (see subsection "Linkage Dysequilibrium" later in this section).

Copy number variation (CNV) describes chromosomal regions in which one or more genes are deleted or occur in multiple copies.

Insertion/deletion polymorphisms are microscopic insertions and deletions of one to hundreds of base pairs and are much smaller than CNVs.

Microsatellites are a type of polymorphisms, also called *short tandem repeats* (STRs) or *variable number of tandem repeats* (VNTRs). About 30,000 of these polymorphisms exist in the human genome, and they serve as markers for genome-wide linkage analysis (see "Linkage Studies" subsection later in this chapter for more detail).

Single nucleotide polymorphisms (SNPs) consist of a single base difference at a particular site in the genome, commonly a cytosine-to-thymine (C-to-T) exchange. Most SNPs have two alleles, but SNPs with three or four different alleles have been reported.

Molecular Genomic Variation in Psychiatric Disorders

Psychiatric disorders are complex genetic disorders. Genetic epidemiological studies have established that psychiatric disorders are not single-gene disorders inherited in a *Mendelian fashion* (i.e., in a clear recessive, dominant, or X-linked fashion), although there are rare families in which psychiatric phenotypes are inherited in this way (Brunner *et al.* 1993). A genetic disorder can be complex for several reasons, as outlined in Table 3-2. In the following sections, we describe different types of genetic variants and specific examples linking them to psychiatric disorders and traits. Table 3-3 focuses on larger variants observable at the chromosomal level, including translocations and larger deletions.

TABLE 3-2. Complexity of genetic disorders

---

* *Incomplete penetrance*. Not every person carrying the disease allele(s) has symptoms.

* *Phenocopy occurrence*. Nonheritable traits caused by environmental factors can resemble traits caused by a genetic mutation.

* *Locus heterogeneity*. Variants in different genes can lead to similar or identical disease phenotypes.

* *Allelic heterogeneity*. Different patterns of variation within the same gene or genes can lead to similar or identical disease phenotypes.

* *Polygenic inheritance*. Additive or interactive effects of variation at multiple genes (i.e., epistatic effects) are necessary for an illness to manifest.

* *Gene-by-environment interaction*. A disorder manifests in response to environmental factors only in the context of predisposing genetic variants. An extreme example of such interaction is phenylketonuria, in which exposure to dietary phenylalanine causes severe neurobehavioral impairment in individuals carrying two mutant copies of the locus encoding phenylalanine hydroxylase; limitation of dietary phenylalanine prevents the neurobehavioral disorder.

* *High frequency of the disorder and the predisposing alleles*. It appears increasingly likely that common disorders represent final common outcomes of a variety of combinations of environmental and genetic predisposing factors. Thus, two individuals, even within the same family, might manifest clinically indistinguishable disorders for different underlying reasons.

* *Other genetic mechanisms of inheritance*. Alternative genetic mechanisms--for example, mitochondrial inheritance or alteration of the genome across generations, such as occurs in trinucleotide-repeat-expansion disorders (e.g., Huntington's disease and fragile X syndrome) or in epigenetic disorders--may be involved in producing a disorder. Epigenetic disorders result from alterations in the genetic material that do not involve changes in the base-pair sequence of DNA. Examples of epigenetic disease include the imprinted disorders Angelman syndrome and Prader-Willi syndrome, in which parent-of-origin-dependent

chemical modification of DNA produces different phenotypic outcomes from the same chromosomal deletion.

TABLE 3-3. Larger genetic variants observable at the chromosomal level

Variation in chromosomal number

The human genome has approximately 3 billion bases that are distributed over 23 chromosome pairs, with 22 pairs of autosomes and 1 pair of sex chromosomes, X and Y. The most obvious genetic variations can be observed at the light microscope level in the karyotype. This approach visualizes metaphase chromosomes using histological procedures, allowing identification of each specific pair of chromosomes and variations in the total number of chromosomes, such as unisomies and trisomies.

Translocations

Karyotypic examination and other cytogenetic techniques such as fluorescent in situ hybridization (FISH) can detect large-scale chromosomal abnormalities, such as translocations, deletions, or duplications of large regions of chromosomes. In a large Scottish pedigree, a balanced translocation between chromosomes 1 and 11 appears to be causally linked to a series of major psychiatric disorders, including schizophrenia, bipolar disorder, recurrent major depressive disorder, and conduct disorder (St Clair *et al.* 1990). This *balanced translocation* (which exchanged parts of chromosome 1 with parts of chromosome 11 to produce two abnormal chromosomes but no net loss of chromosomal material) disrupts two genes at the translocation breakpoint on chromosome 1, termed *disrupted in schizophrenia* (*DISC*) *1* and *2* (Millar *et al.* 2000, 2001). Subsequent molecular analysis has provided strong evidence that variation in *DISC1* can alter the risk for schizophrenia (Porteous *et al.* 2006).

Deletions

Microdeletions occurring on the long arm of chromosome 22 have received considerable attention as cytogenetic risk factors for the development of schizophrenia (Karayiorgou and Gogos 2004). In the 22q11 deletion syndrome, 1.5-3.0 million base pairs (bp) of DNA are missing on one copy of 22q. There is a reported 10-20 times higher prevalence of the 22q11 deletion in patients with schizophrenia (Rees *et al.* 2014b), and duplications of 22q11.2 might prove protective (Rees *et al.* 2014a).

Duplications

Duplications of the long arm of chromosome 15 (15q11-13) are the most frequent cytogenetic anomalies in autism spectrum disorder (ASD), occurring in approximately 1%-2% of cases (Cook 2001). This duplication syndrome cannot be clinically differentiated from idiopathic autism (Veenstra-VanderWeele and Cook 2004), indicating that a complete workup of ASD should include testing for this cytogenetic abnormality as well as several others (Martin and Ledbetter 2007). Interestingly, deletion of this same region of 15q is associated with Angelman syndrome when the deletion occurs on the maternal copy of chromosome 15 and with Prader-Willi syndrome when the deletion occurs on the paternal chromosome.

Copy Number Variations

Rare CNVs in specific chromosomal locations have been associated with a strongly increased risk for neurodevelopmental disorders, including autism spectrum disorder (ASD) and developmental delay, as well as schizophrenias. These rare CNVs include deletions at 1q21.1, *NRXN1*, 3q29, 15q11.2, 15q13.3, and 22q11.2, and duplications at 1q21.1, 7q11.23, 15q11.2-q13.1, 16p13.1, and proximal 16p11.2. They are very rare in the general populations but are observed cumulatively in a percentage of the above-named disorders with a strong penetrance and odd ratios to develop the disorder of up to 50-fold or more. In most cases, these CNVs include more than one gene (Kirov 2015; Rees and Kirov 2021).

CNVs of the cytochrome P450 (CYP) genes, including *CYP2D6*, which are important for the metabolism of many antidepressants, antipsychotics, and mood stabilizers (Kirchheiner *et al.* 2004), provide a prominent example of the importance of CNVs to pharmacogenetics (Santos *et al.* 2018). The reported range of copy numbers of *CYP2D6* is from 0 to 13. The number of functional copies of *CYP2D6* directly negatively correlates with plasma levels of metabolized drugs, such as the tricyclic antidepressant nortriptyline (Bertilsson *et al.* 2002). It is important to bear in mind the population-specific frequencies (Santos *et al.* 2018) and to continue investigating specific subgroup populations (Ramirez *et al.* 2019).

Insertion/Deletion Polymorphisms

Among the most famous insertion/deletion polymorphism in psychiatric genetics is a common functional polymorphism in the promoter region of the serotonin transporter gene, *SLC6A4*, referred to as the serotonin transporter-linked promoter region (5HTTLPR) (Gelernter *et al.* 1999; Heils *et al.* 1996; Lesch *et al.* 1996; Nakamura *et al.* 2000). The 5HTTLPR has been associated with altered basal activity of the transporter, most likely related to differential transcriptional activity (Heils *et al.* 1996; Lesch *et al.* 1996) or differences in serotonin transporter binding potential (Parsey *et al.* 2006). It has been associated with increased risk for many psychiatric disorders, mainly mood and anxiety disorders; treatment response to antidepressant drugs, mainly selective serotonin reuptake inhibitors; and the moderation of adversity and stress-related psychiatric risk, although larger meta-analyses do not always support findings from the initial smaller studies (e.g., Crawford *et al.* 2013; Culverhouse *et al.* 2018).

Variable Number of Tandem Repeats

VNTRs not only serve as genetic markers for linkage analysis but also may produce functional variation within genes by altering gene regulatory elements and thus gene expression levels. Such VNTRs have been identified in a number of genes--including genes of the dopaminergic system, such as the dopamine transporter (DAT) gene *SLC6A3*, the *DRD4* locus encoding the dopamine D_4 receptor, and the dopamine b-hydroxylase gene (*DBH*), as well as the monoamine oxidase A gene (*MAOA*)--and associations with many psychiatric, behavioral, and brain phenotypes have been reported (Gatt *et al.* 2015). However, medium to strong functional effects on gene regulation have been confirmed only for *DBH* and *MAOA*. Both polymorphisms have been associated with a multitude of behavioral and psychiatric phenotypes (Tunbridge *et al.* 2019).

Single Nucleotide Polymorphisms

The discovery of SNPs has revolutionized psychiatric genetics among other fields (Altshuler *et al.* 2000; Sachidanandam *et al.* 2001). By 2020, more than 2 billion human SNPs had been catalogued in public databases (e.g., dbSNP; www.ncbi.nlm.nih.gov/projects/SNP). SNPs are the most common type of genetic variation and may represent up to 90% of all genetic variations. Besides being very frequent in the genome (SNPs occur, on average, every 300 bases), they are also amenable to high-throughput genotyping methods (Kim and Misra 2007; Kwok 2000). Since SNPs are common (essentially each gene of interest has several known SNPs) and cheap to genotype, they represent the markers of choice for complex trait genetic association studies that now cover the whole genome in so-called genome-wide association studies (GWAS).

Besides serving as genetic markers for chromosomal loci in association studies, SNPs also can have functional relevance themselves. SNPs in regulatory regions can alter the transcriptional regulation of a gene, SNPs in regions relevant for messenger RNA (mRNA) splicing can alter splice sites, and SNPs in protein-coding exons can encode differences in the primary amino acid sequence. Interestingly, when one considers the occurrence of SNPs across the genome, one observes that SNPs are most dense in intergenic and intronic regions but scarcer in putative regulatory regions and exons, suggesting selection against putatively functional genetic variants (Altshuler *et al.* 2000; Sachidanandam *et al.* 2001). Within exons, SNPs that do not cause an amino acid exchange due to the degenerate code are called synonymous SNPs, as opposed to nonsynonymous SNPs, which lead to amino acid substitution. One nonsynonymous SNP that has been associated with psychiatric phenotypes is the catechol-O-methyltransferase gene (*COMT*) polymorphism Val^{158}Met affecting the temperature lability of this enzyme's activity (Lachman *et al.* 1996; Lotta *et al.* 1995). The Val/Val genotype more rapidly inactivates, following an additive genetic model. This SNP seems to affect dopamine transmission--particularly in the frontal cortex, where expression of the dopamine transporter protein is relatively low--and has been associated with differences in executive cognition and functional activity of the prefrontal cortex during working-memory tasks (Egan *et al.* 2001; Goldberg *et al.* 2003; Joober *et al.* 2002; Mattay *et al.* 2003). Although it was hypothesized that this polymorphism also could alter the risk for schizophrenia (particularly because *COMT* resides in the 22q11 region, the deletion of which has been associated with schizophrenia), larger association studies and meta-analyses do not fully support that conclusion (Fan *et al.* 2005; Farrell *et al.* 2015; Okochi *et al.* 2009).

Identification of Risk Loci for Psychiatric Disorders

From the cumulative evidence of psychiatric genetic studies, including the molecular studies discussed in detail below, one can conclude that psychiatric disorders fit a

polygenic model of inheritance, with many polymorphic loci of low effect size contributing to disease risk in a mainly additive fashion (Wray *et al.* 2018).

In the following subsections, we describe methods for identifying these genetic loci associated with psychiatric disease risk. We first explain cytogenetic studies and linkage studies and then focus on what is now the most commonly used identification method: association studies.

Cytogenetic Studies

Disruption of chromosomal integrity by rare events such as balanced translocations has facilitated gene discovery in a variety of diseases and holds significant promise for similar applications in psychiatric illness (Pickard *et al.* 2005). Advances in techniques such as chromosome painting, high-resolution fluorescent in situ hybridization (FISH), and, most recently, genome-wide analysis of copy number variations using microarrays have made it possible to identify disruptions in chromosomal architecture to single-base resolution, thus facilitating identification of specific genes in families cosegregating mental illness and cytogenetic abnormalities. Such data then may be used to generate testable hypotheses about the role of a particular gene in disease pathophysiology. The *disrupted in schizophrenia* (*DISC*) *1* and *2* genes provide clear examples of specific genes implicated in mental illness following their discovery through careful molecular analysis of a cytogenetic anomaly.

Linkage Studies

In the 1980s and 1990s, many genes for Mendelian disorders were successfully identified with linkage analysis in large families. Linkage relies on the principle that, on average, chromosomes from parents differ from those of offspring by only one meiotic crossover event. During *meiosis*--the cell divisions that produce gametes by reducing the diploid genome (i.e., two chromosomes of each pair per cell) to a haploid genome (one copy of each chromosome per spermatocyte or ooctye)--homologous grandparental chromosomes (i.e., paternal and maternal to the parents of the offspring of interest) make physical contact and exchange homologous regions (referred to as *crossing over*) to give rise to a new set of chromosomes in which each gametic chromosome is a mix of grandparental sequences. This crossing-over process produces recombinations that can then be tracked with molecular markers to delineate the ancestral origin of each chromosomal region in the offspring.

Classically, linkage studies use from several hundred to a few thousand microsatellite markers, evenly spaced across the genome. These markers are then genotyped in large families in which the disease of interest is common. To identify positions in the genome that may be involved in the disease, one tracks whether marker alleles are inherited by affected relatives more often than would be expected by chance (i.e., linkage tests whether a particular chromosomal region cosegregates with the disease). A quantitative measure of the likelihood of a particular pattern of marker-disease cosegregation is the *logarithm of odds* (LOD) score, with a LOD score of 3.3 or greater being required before significant linkage is accepted (Lander and Schork 1994). Classical linkage approaches have been very successful in identifying monogenic diseases that follow clear, simple patterns of inheritance, but they have been far less successful in complex psychiatric disease.

Association Studies

While linkage studies allow the investigation of whether a variant segregates with a disease or phenotype in a pedigree, association studies can investigate whether a variant is more or less common in cases versus controls or if it associates with a quantitative trait. Given the complex, polygenic inheritance of psychiatric disorders, this method in now the most commonly used in psychiatric genetics. To help interpret association studies, we first need to introduce two key concepts, which are important for their design and understanding: linkage disequilibrium and population stratification.

Linkage Disequilibrium

GWAS rely on the principle that even unrelated individuals share very small stretches of chromosomal DNA derived from a distant common ancestor. In the case of a disease-predisposing mutation, some proportion of ill individuals will share that mutation arising from an original common ancestor. As the variant is passed down from generation to generation, meiotic recombination events will shrink the size of the initial piece of ancestral chromosome that is inherited together with the disease mutation. On these small ancestral stretches of chromosome (perhaps several thousand to several hundred thousand base pairs in length), nonfunctional "marker" polymorphisms close to the disease mutation will "ride" through generations together with the disease variant. Such markers (e.g., SNPs) thus can serve as surrogate "tags" for the disease mutation. Note, however, that as generations pass and individuals become ever more distant relatives (to a point when the social/cultural "memory" of the genetic relationship is usually lost), different families will produce recombination events at different points near the disease mutation. Therefore, at a population level, unrelated individuals carrying the disease marker will carry variable lengths of DNA upon which markers linked to the disease variant ride. Stated another way, unrelated individuals carrying the disease variant will carry haplotypes that become more similar to one another as the boundaries of the haplotypes are moved closer to the disease variant. Thus, the closer a marker is to the disease variant, the more likely it is to be originally linked to the variant. When a marker is close enough to a disease marker that the number of recombination events in the population has not yet completely randomized, and the odds are high that it is on the same ancestral stretch of DNA (haplotype) as the disease variant, the marker and the disease variant are correlated and are said to be in *linkage disequilibrium* (LD). Knowing the allele of a marker variant in LD with a disease variant can therefore allow one to predict the allele of the disease variant (i.e., the marker and the disease variant are not statistically independent).

Several factors influence the length of DNA over which LD occurs. The most important are the geographic origins of the population from which an individual is drawn and the history of that population. For example, sub-Saharan African populations are ancient and reflect the greatest proportions of the total human pool of variation, because most of the history of the human species predates migration of humans out of Africa. Therefore, on average, sub-Saharan African populations have undergone the greatest number of recombination events since a given pair of unrelated individuals shared a common ancestor. Those individuals thus share only short stretches of ancestral chromosomes (which are said to be *identical by descent*, or IBD). Non-African populations all derive from a relatively small number of migrants who left Africa within approximately the last 100,000 years. Thus, Europeans, Eastern Asians, or Native Americans share longer stretches of DNA IBD within their respective continental groups than do sub-Saharan Africans (Daly *et al.* 2001; Gabriel *et al.* 2002; Patil *et al.* 2001; Reich *et al.* 2001). At the other extreme, individuals from reproductively isolated populations, in which a small founder population has expanded with little admixture (i.e., introduction of outside individuals into the mating pool), share longer blocks of ancestral chromosomes that are IBD (Shifman and Darvasi 2001). An example is the Icelandic population, which derives almost exclusively from a small number of migrants who arrived on the island only several hundred years ago (Helgason *et al.* 2003).

Another factor contributing to the complexity of patterns of LD is the fact that recombination events do not occur with the same likelihood across all parts of the genome (Phillips *et al.* 2003; Reich *et al.* 2002). In addition to a general pattern, in which more telomeric regions of chromosomes are more likely to recombine than centromeric regions, specific "hot spots" of recombination have been identified that are spaced unevenly along chromosomes. This variation across the genome in the likelihood of recombination results in the observation that certain stretches in the genome (sometimes referred to as blocks) have undergone relatively little recombination over the generations and therefore show strong LD among SNPs in the region. Such regions of high LD can span millions of bases, whereas other regions in the same population have recombined more frequently, resulting in very short blocks of LD (e.g., < 5,000 base pairs). Within a block of LD, alleles of adjacent variation thus do not co-occur in random patterns but can be predicted and form a limited number of haplotypes (much less than the statistically possible combination of all alleles of all variations in the LD block). For this reason, such regions of high LD are also called *haplotype blocks* (Daly *et al.* 2001; Gabriel *et al.* 2002; Patil *et al.* 2001; Reich *et al.* 2001).

To date, there remains a huge diversity issue in genetic studies, with a massive overrepresentation of GWAS carried out in European populations (Popejoy and Fullerton 2016). The ethnicity of the study population must always be taken into consideration; although Mendelian (monogenic) disorders may cross populations, oligogenic or polygenic disorders will have limited transfer (Curtis 2018). A variant may be tagged by different SNPs in different ethnicities (allelic heterogeneity). When risk is assessed by tagging SNPs, LD strength will affect associations across populations.

From the Human Genome Project came HapMap (genotyping) and subsequently the 1000 Genomes Project (next-generation sequencing), which catalogue human genetic variations. These projects describe LD structures, providing a high-resolution map of the landscape of human genetic variation. Today, the richest database is the Genome Aggregation Database (gnomAD; http://gnomad.broadinstitute.org), which holds 15,798 whole genomes and 125,748 exomes. The newly released version 3.0 (2021) contains more than 76,000 genomes from various populations (Karczewski *et al.* 2020). These catalogs are all publicly available genomic datasets and have provided validation for many SNPs in databases such as the dbSNP.

Population Stratification

Frequencies of specific alleles can vary to a large degree among different populations. Spurious associations can thus be found if subjects for a genetic association study are

sampled from multiple subpopulations with different genetic ancestries (and thus with different allele frequencies in specific loci) in different proportions in case and control participants. Differences in allele frequencies between comparison groups can thus result from differences in the population structure of the sample alone, without any causal relationship to the outcome of interest. This problem is called *population stratification* and is exemplified by the hypothetical example of the "chopsticks gene" (Hamer and Sirota 2000).

Several methods have been developed to address population stratification in genetic association studies. Family-based approaches to genetic association studies, such as the transmission disequilibrium test

(TDT; Spielman *et al.* 1993) and the haplotype-relative risk (HRR) method (Knapp *et al.* 1993), are robust to population stratification. Population stratification cannot arise because each family provides its own control, and because the proband is always matched for the population background of the parents, population stratification cannot arise. However, such family designs are often not practical for large-scale studies or studies with late disease onset.

To control for population stratification in case-control studies, several methods have been suggested. The most commonly used method nowadays involves the use of genome-wide genotype data combined with principal component analysis to identify population substructures (Price *et al.* 2006). First, a matrix across all sample pairs reflecting the number of identical genotypes per pair is constructed. Second, the main axes of genome-wide genetic variation, also called *principal components*, of this matrix are calculated and plotted against each other to identify possible population outliers or clusters. These main (principal) components are then included as covariates in subsequent association analyses to correct for population admixture. Principal component maps are used to show how genetic similarity declines with geographical distance (see Novembre and Stephens 2008 for more details).

Genome-Wide Association Studies

The knowledge of the human genome and of its linkage disequilibrium structure, as well as technological advances, has made it possible to test genome-wide genetic association for psychiatric traits and disorders on a large scale. Both methods using array technology for genotyping and next-generation sequencing methods are used and can be applied in very large cohorts, with costs of genome-wide SNP genotyping arrays well below 50 US$ and genome-wide sequencing approaches below 600 US$ per sample.

How Many SNPs Are Needed?

The presence of linkage disequilibrium in the human genome allows investigators to evaluate a large extent of the common genetic variation through a much-reduced number of selected markers. Thanks to the catalogues of human genetic variation outlined earlier in this chapter, the genetic variability of the entire genome can be covered to a reasonable extent using SNP arrays. SNP arrays are high-throughput DNA microarrays that measure selected SNPs and small CNVs that tag LD blocks across the genome. Using the data from several hundred thousand SNPs is thus sufficient to cover most common variants in Europeans; more variants are necessary in African populations with shorter LD blocks (for a review, see Hirschhorn and Daly 2005). The genotypes of these tag variants can then be used to infer the genotypes at all known

sites with similar allele frequencies using imputation algorithms. *Genotype imputation* refers to a method that estimates genotype probabilities of SNPs that are missing in the study population, because of quality control or because they have not been covered by the used genotyping arrays. This estimation is based on reference samples such as the HapMap or the 1000 Genomes Project. These reference samples have been sequenced genome-wide, and hence a high number SNP genotypes is available. There are a variety of imputation tools that can be used (for more details, see Shi *et al.* 2018). In all of these methods, probabilities of SNP genotypes in the study population are estimated based on the LD structure between SNPs in the reference sample. Usually, estimated genotypes of those SNPs that could be predicted with a high probability are then used for further association analysis. Naturally, this estimation works well in regions of the genome in which a lot of SNPs in high LD are present. Furthermore, the reference sample and study sample should be from the same ethnic background; otherwise, LD patterns in the reference sample might not reflect the LD structure of the study sample.

A major drawback of whole-genome LD-based array approaches to association testing is that most sequence variation in the genome is rare, and rare variants are not tagged to the same extent as the more common variants (allele frequencies over 1% in a given population) on current arrays. Thus, to the degree that the genetic underpinnings of complex disease deviate from the "common disease, common variant" hypothesis, whole-genome SNP scans will be inadequate to detect all associated genes (Zwick *et al.* 2000). This concern is not merely theoretical, because rare variants also clearly contribute to complex disease--most notably ASD (Satterstrom *et al.* 2020). In all likelihood, complex disorders represent a mixture of contributions from rare and common variants, so that methods appropriate for both types of variation will need to be implemented.

Whole-genome sequencing, or the more focused approach of whole-exome (only the RNA/protein coding part of the genome) sequencing, has yielded important insights into the contribution of rare variants to most psychiatric disorders (Satterstrom *et al.* 2020; Takata 2019; Xu *et al.* 2011).

How Many Individuals Are Needed?

Genome-wide associations require a massive correction for multiple testing, so *P* values less than 5×10^{-8} have to be achieved for an association to be considered genome-wide significant. These necessarily low alpha levels, together with the expected low ORs associated with identified common susceptibility variants or the extremely low allele frequency of rare variants, require large sample sizes for adequate power. When one surveys genome-wide association discoveries over time, it can be seen that the larger the sample size, the more genome-wide association hits are found (see Figure 2 ["Increase in Number of Loci Identified as a Function of Experimental Sample Size"] in Visscher *et al.* 2012; www.ncbi.nlm.nih.gov/pmc/articles/PMC3257326/figure/fig2). Since 2009, the number of genomic loci found to be associated with schizophrenia, for example, has risen dramatically as a result of ever more cases being available, and discovered loci increased from zero in 2009 to 248 in 2020 (Table 3-4).

TABLE 3-4. History of studies identifying schizophrenia (SCZ) associated loci (at least one genome-wide association study single nucleotide polymorphism in the discovery meta-analysis)

Study	Year	Number of SCZ cases	Number of loci

Study	Year	Number of SCZ cases	Number of loci
International Schizophrenia Consortium (Purcell *et al.* 2009)	2009	2,601	0
Psychiatric Genomics Consortium--Wave 1 (Schizophrenia Psychiatric Genome-Wide Association Study Consortium 2011)	2011	8,228	3
Ripke *et al.* 2013	2013	12,971	11
Psychiatric Genomics Consortium--Wave 2 (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014)	2014	35,476	97
Lam *et al.* 2019	2019	56,418	176
Psychiatric Genomics Consortium--Wave 3 (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2020)	2020	67,390	248

Source. Adapted from Schizophrenia Working Group of the Psychiatric Genomics Consortium 2020.

Power (i.e., the probability of obtaining a true-positive result) is determined by sample size, allele frequency, effect size, and significance level. For example, considering a quantitative trait and setting the alpha level to 5 x 10^{-8}, more than 10,000 individuals would be needed to detect a variant that explains 0.2% of the variance with a power of at least 80% (Visscher 2008). Current GWAS now often include more than 100,000 individuals. These sample sizes can be reached only within consortia that combine samples from many different studies and meta-analyze them together, such as the Psychiatric Genomics Consortium, a large-scale international collaboration (www.med.unc.edu/pgc) that continues to advance genetic discovery in psychiatry (Sullivan 2010). The Psychiatric Genomics Consortium has many working groups for the various psychiatric disorders and psychiatric traits as well as cross-disorder working groups. Other sources include large population-based initiatives, such as the UK Biobank (www.ukbiobank.ac.uk) and the All of Us Research Program (Sankar and Parker 2017); cohorts based on military personnel, such as the Million Veteran Program (www.mvp.va.gov/pwa); and research collaborations with large direct-to-consumer DNA testing companies, such as 23andMe (www.23andme .com/en-int). A number of Scandinavian countries now allow researchers to combine large-scale genotyping efforts with registry-based data on disease and exposure (e.g., iPsych in Denmark [Pedersen *et al.* 2018] and the Norwegian Mother, Father and Child Cohort Study [MoBa; www.fhi.no/en/studies/moba]). Another possibility is the use of electronic health records (EHRs), which are commonly used in health care systems, particularly in the United States (Dewey *et al.* 2016; Rader and Damrauer 2016). Some of these records have genomic data linked and as such provide new opportunities for population-based studies in psychiatry, with some studies already indicating good predictive value with diagnostic algorithms (Smoller 2016). The PsycheMERGE consortium was specifically formed to utilize EHRs for genetics research (Crawford *et al.* 2014).

Cross-Disorder Studies

Disorder-specific GWAS have by now identified robust genetic hits for all diagnoses, led in number by more than 200 independent genetic loci associated with schizophrenia.

It has become increasingly clear that most psychiatric disorders share genetic risks, as indicated in family studies. The genetic architecture correlation calculated from common SNPs is high (r = 0.68 for bipolar disorder and schizophrenia, r = 0.47 for bipolar disorder and depression, and r = 0.43 for schizophrenia and MDD) (Cross-Disorder Group of the Psychiatric Genomics Consortium *et al.* 2013). A study investigating the genetic overlap of brain disorders using GWAS of 265,218 patients and 784,643 control subjects observed that psychiatric disorders overall shared genetic risk, with a correlation of 0.41 across these disorders, whereas the neurological disorders were genetically more distinct from each other (Anttila *et al.* 2018).

Attempts have been made to identify the underlying molecular source of the genetic overlap across disorders (i.e., those genetic variants shared across disorders). The Cross-Disorder Group of the Psychiatric Genomics Consortium *et al.* (2013) initially examined five disorders (i.e., schizophrenia, MDD, bipolar disorder, ASD, and ADHD) in a combined sample of more than 33,000 case participants and over 27,000 control participants. Findings from these cross-disorder studies confirmed the biological overlap of psychiatric traits. Four loci with genome-wide significance for cross-disorder risk were found, including the L-type voltage-gated calcium channel subunits CACNB2 and CACNA1C, again implicating calcium channels in psychopathology. This investigation has recently been expanded to include patients with anorexia nervosa, OCD, and Tourette syndrome, for a total of more than 230,000 case participants and close to 500,000 control participants. Here, differing genetic correlations among groups of disorders were noted, with strong correlations between schizophrenia and bipolar disorder and also between anorexia nervosa and OCD, for example, but these latter two disorders are less correlated with schizophrenia and bipolar disorder. Overall, more than 100 loci are associated with at least two disorders, and more than 20 with four or more disorders, providing strong support for specific patterns of shared genetic risk (Lee *et al.* 2019).

Computational Techniques Using GWAS Summary Statistics

Polygenic Risk Scores

Already with early GWAS, it became clear that in complex disorders, genetic risk is determined both by many common variants of small effect and by rare and de novo variants of large effect.

This dilemma again illustrates the inadequacy of the "common disease, common variant" model and the limitations of GWAS. As a result, it has been proposed that between these two extremes, there is a middle ground in which moderately penetrant but somewhat rarer variants are being missed (Maher 2008). These missing variants might be unearthed if a single polygenic score or polygenic risk score (PRS) could be calculated. Polygenic analysis examines the extent to which heritability is due to the additive effects of many common loci variants that individually are of little effect (Dudbridge 2013). By using all SNPs to examine the net effect on disease risk, a composite score can be calculated, thus providing significant predictive ability. The PRS is composed of many true but subthreshold variants that GWAS initially might have missed as a result of being underpowered to detect them at the conventional alpha level of $P = 5$ x 10^{-8} (Gratten *et al.* 2014). Polygenic risk profiling from large GWAS is able to predict case-control status in independent, and also smaller, samples. The PRS also can be analyzed in relation to the clinical phenotype and against quantitative traits related to the disorder.

This approach was validated, for example, in schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) and has been shown to predict schizophrenia case-control status in a number of independent samples (Meier *et al.* 2016), with risk increased up to 15-to 20-fold for individuals in the highest polygenic risk score decile. Similar approaches have been applied to other disorders. For MDD, individuals in the highest polygenic risk decile have a 2.0-to 2.5-fold increased risk (Wray *et al.* 2018). Such PRSs could be promising biomarkers to guide clinicians in diagnosis, treatment choice, and prediction of disease course. Such risk scores may also be used to identify individuals at high risk for psychiatric disease before disease onset for targeted preventions and early intervention. In fact, the use of PRSs as predictors in clinical care has been proposed for medical disorders (Khera *et al.* 2018; Lambert *et al.* 2019).

An important step for clinical application is to understand whether PRSs derived in a research setting can be applied to real-world clinical settings. Zheutlin *et al.* (2019) have explored this question by applying the PRS for schizophrenia (derived from samples collected in a research setting) to EHR data from four different health care system-based biobanks. The authors could predict psychosis and schizophrenia using the PRSs in these datasets, but with lower ORs than in studies from research settings. Individuals in the top decile of PRSs had a 2.0-to 4.5-fold increased risk. These effects sizes are comparable to those observed for medical disorders (Khera *et al.* 2018), suggesting that genetic prediction strategies may also be applied to psychiatry. Although highly statistically significant, the effects of the PRS were not sufficiently large to allow an accurate discrimination of patients.

The PRS is a promising tool, but many open questions need to be addressed before it can be applied in the clinical setting:

1. PRSs developed in one ancestral group will not directly extend to another, and so far the vast majority of GWAS have been conducted in populations of European ancestry. For example, PRSs for schizophrenia calculated based on association results in one population are significantly less predictive in another. Performing GWAS in non-European populations is a great need (Duncan *et al.* 2019) and is necessary for their application in a global clinical setting.
2. Shared genetic heritability among psychiatric and also neurological and medical disorders (Anttila *et al.* 2018) poses problems for applying PRSs as clinical tools. The schizophrenia PRS additionally associates with risk for PTSD, bipolar disorder, and other psychiatric disorders, with CIs of ORs mostly overlapping with those of ORs for schizophrenia and psychosis, and the same PRS is also associated with some medical conditions. Such pleiotropy in prediction raises issues for clinical implementation.
3. PRSs developed in one specific clinical context, such as adult patients, may not perform in other contexts (e.g., younger individuals).
4. PRSs may need to be combined with information on other risk domains to improve prediction. In medical disorders, multimodal prediction models that integrate PRSs (Lambert *et al.* 2019) perform better than those that do not. A PRS for

coronary artery disease, for example, increases the accuracy of established clinical predictors, such as the Framingham Risk Score (Abraham *et al.* 2016).

5. For medical disorders, it has been proposed that the PRS may be most useful for prevention (Lambert *et al.* 2019). In children with a family history of type 1 diabetes, for example, a PRS for this disorder was able to predict progression to diabetes before any metabolic abnormalities were present (Redondo *et al.* 2018). Such an application may be relevant for youths at high risk for psychiatric disorders and inform targeted prevention and interventions studies.

In addition to PRSs, a number of computational tools are now available to increase our understanding of genetic factors in psychiatry. These include the following:

- *Mendelian randomization*, which enables an assessment of potential causality in the association between two traits based on Mendel's law that the genetic variants associated with these traits are inherited independently, thus providing a "natural" randomized controlled trial (RCT) (for a review, see Wootton *et al.* 2022). Here one of the traits can also be molecular phenotypes, such as the effects of SNPs of immune measures, mapped to GWAS for a disease of interest (Kappelmann *et al.* 2021). This procedure allows one to test whether changes in immune function are causally related to depression, for example, via their shared genetics.
- *Transcriptome-wide association studies (TWAS)*, which combine both GWAS and gene expression datasets to understand the effect of genetic risk on the transcriptional profile of a target tissue, and thus its potential impact on function (for further detail, see Hernandez *et al.* 2021 and Wainberg *et al.* 2019).
- *Phenome-wide association studies (pheWAS)*, which allow one to explore the genetic association of a more limited number of genetic variants with a large number of phenotype datasets (e.g., EHRs), permitting detection of novel genetic overlaps of phenotypes (see Bush *et al.* 2016 and Wang *et al.* 2021).

From Association to Function--Approaches to Using the Data

While GWAS have yielded many associated loci, they do not directly allow an understanding of the underlying biology. Figure 3-3 illustrates the steps from an association study to improved functional understanding. Excellent reviews on this topic are available (see, e.g., Fernando *et al.* 2020; Uffelmann and Posthuma 2021); we briefly summarize the most relevant steps below.

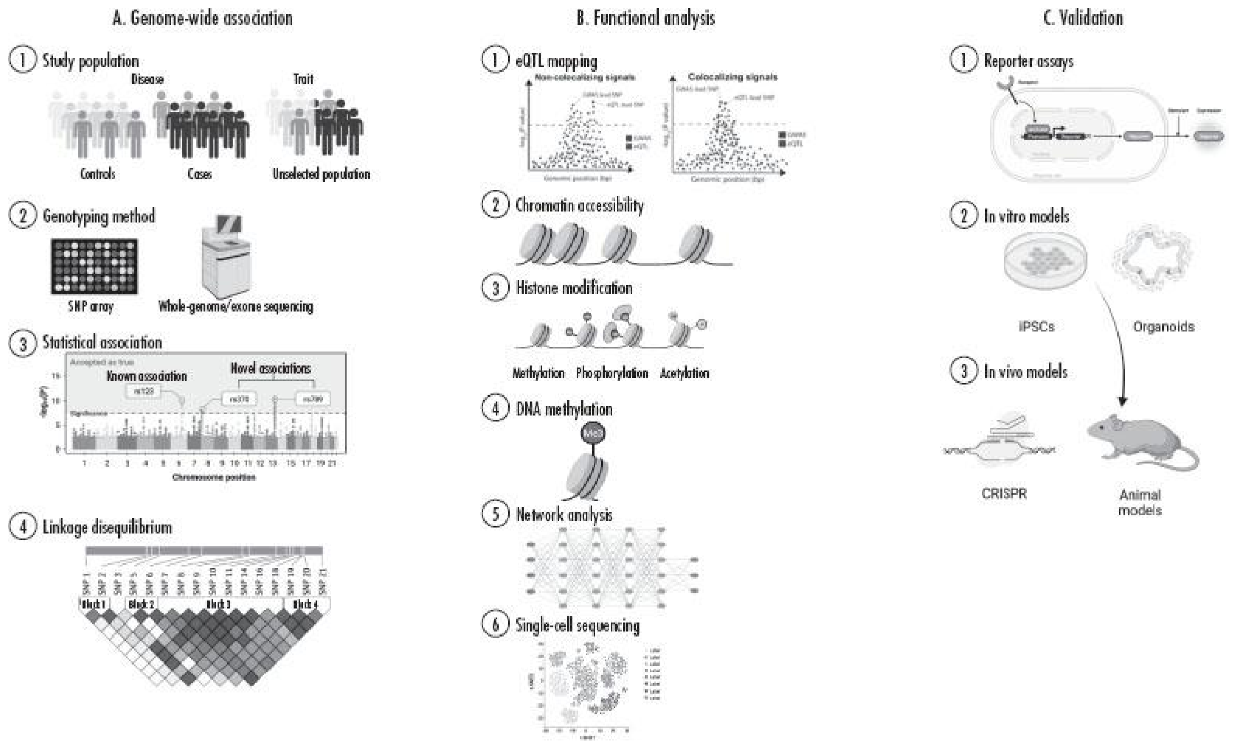
A. Genome-wide association
① Study population
Disease
Trait
Controls
Cases
Unselected population
② Genotyping method
SNP array
Whole-genome/exome sequencing
③ Statistical association
Known association
Novel associations
rs123
rs370
rs789
Chromosome position
④ Linkage disequilibrium
Block 1
Block 2
Block 3
Block 4
B. Functional analysis
① eQTL mapping
Non-colocalizing signals
Colocalizing signals
② Chromatin accessibility
③ Histone modification
Methylation
Phosphorylation
Acetylation
④ DNA methylation
Me3
⑤ Network analysis
⑥ Single-cell sequencing
C. Validation
① Reporter assays
② In vitro models
iPSCs
Organoids
③ In vivo models
CRISPR
Animal models

FIGURE 3-3. From association to function *(previous page)*.

See Plate 22 to view this figure in color

(A) Genome-wide association studies (GWAS) are used to detect associations between a specific phenotype and the frequency of single nucleotide polymorphisms (SNPs). ***(1) Study population*** selection. Cases and controls can be compared for disease associations, or a population can be used to measures associations with quantitative traits. ***(2) Genotyping methods*** include SNP arrays and whole-genome/exome sequencing. ***(3) Statistical tests*** (in this case a Manhattan plot) can be used to detect associations between regions of the genome and the trait of interest. ***(4)*** Genotyped SNPs are in ***linkage disequilibrium*** (LD) with causal variants. This panel shows an LD matrix plot, where the color intensity is proportionate to linkage strength. **(B) Functional analysis of genetic variants.** Epigenetic investigations include the following: ***(1) Expression quantitative trait locus (eQTL) analysis***. Patterns of associations of GWAS and eQTLs can tell us whether they are both being driven by the same causal variant in LD. ***(2-4)*** Different marks to measure the functionality of regulatory elements: ***(2) chromatin accessibility***, ***(3) histone modification***, and ***(4) DNA methylation***. Me3 = methylation mark. ***(5)*** Gene expression ***network analysis*** allows one to interpret functionality based on gene network correlations. ***(6) Single-cell sequencing*** now allows one to map gene expression profile and QTLs to specific cell types. t-SNE = t-distributed stochastic neighbor embedding. **(C) Validation of findings.** ***(1)*** Genetic variants of interest can be validated using ***reporter assays*** to confirm their regulatory effects. ***(2) In vitro models.*** Induced pluripotent stem cells (iPSCs) and derived cells and organoids allow one to investigate genetic variants in the human context. ***(3)*** Humanized ***animal models*** (using CRISPR [clustered regularly interspaced short palindromic repeats] technologies or by human iPSC-derived cell transplantation) allow one to explore circuit-level and behavioral consequences of specific genetic variants or of cells carrying these variants.

Source. Created with BioRender.com.

As shown in Figure 3-3, GWAS unveil genome-wide significant loci. These are often represented in so-called Manhattan plots (Figure 3-4). In the plot in this figure, each dot represents the association strength of a single SNP, mapped to a negative log of the *P* value, so the higher the peak, the more significant the association. What becomes clear from these plots is that "towers of associations" are observed due to the above-described linkage disequilibrium.

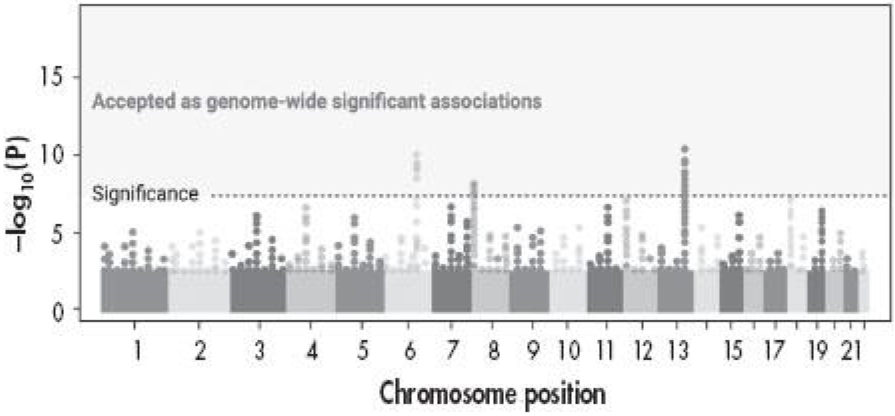

FIGURE 3-4. Manhattan plot.

A Manhattan plot is a specific scatterplot used to display genome-wide association data. Each single nucleotide polymorphism (SNP) is plotted by its position in the genome: the chromosomes of the human genome and the positions on chromosomes are plotted on the x-axis, and the significance of the association with the trait (the [?]$\log_{10}$ of the statistically significant associations) is plotted on the y-axis. The horizontal line shows the standard threshold for genome-wide significance (5×10^{-8}). SNPs are in linkage disequilibrium with the index SNPs (*diamonds*) that represent independent genome-wide significant associations. Schizophrenia was associated with 108 independent loci.

Source. Adapted from "Manhattan Plot for Genome-Wide Association Studies (GWAS)" template, by BioRender.com (2023). Retrieved from https://www.biorender.com/template/manhattan-plot-for-genome-wide-association-studies-gwas.

SNPs in linkage disequilibrium will all show similar associations (depicted in Figure 3-3A, panel 4, with red squares denoting high LD [i.e., high correlation of the SNP genotypes]). Depending on the size of the LD block, a single or many genes can fall under these association peaks, making it very difficult to pinpoint the gene of interest in the absence of additional information. Several steps have been proposed to close in

on the relevant genes from GWAS signals. These include mapping the association signal to molecular quantitative trait loci (QTL), mapping genes to pathways, and mapping SNPs to regulatory elements.

Mapping an association signal to molecular quantitative trait loci.

To understand whether SNPs within an association signal also influence molecular phenotypes, one can use QTL mapping (see Figure 3-3B, panel 1). Often gene expression QTL datasets are used, and many such resources are available online; these include the Genotype-Tissue Expression (GTEx) project (GTEx Consortium 2013), with genotype and RNA sequencing data from close to 1,000 donors and 54 different tissues, including 13 from brain (different brain regions and fetal brain); BrainSpan (Kang *et al.* 2011), with gene expression data from different brain structures across the life span (pre-and postnatal); and the PsychENCODE project (Wang *et al.* 2018; see also, e.g., PsychENCODE Consortium 2018). Use of QTL datasets allows one to see whether an association with disease is also linked to an association with differential gene expression in a specific tissue and, with ever-expanding single-cell sequencing data, in a specific cell type. These types of analyses can additionally be combined in the above-described TWAS. However, QTL mapping can also be performed with other molecular traits, including protein QTL and QTL related to epigenetic regulation, such as DNA methylation QTL and QTL for open chromatin or specific histone modifications (Figure 3-5) (for an in-depth discussion, see Hernandez *et al.* 2021).

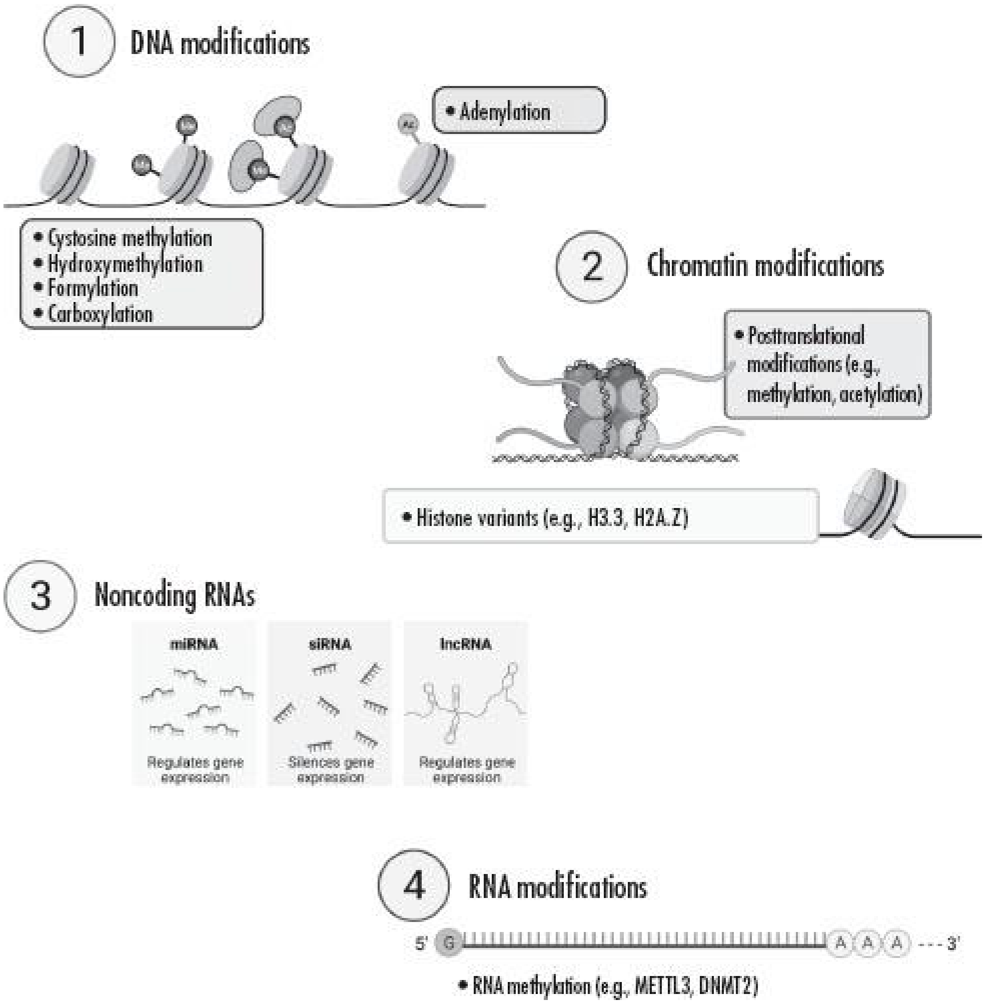
1 DNA modifications
• Adenylation
• Cystosine methylation
• Hydroxymethylation
• Formylation
• Carboxylation
2 Chromatin modifications
• Posttranslational modifications (e.g., methylation, acetylation)
• Histone variants (e.g., H3.3, H2A.Z)
3 Noncoding RNAs
miRNA
Regulates gene expression
siRNA
Silences gene expression
lncRNA
Regulates gene expression
4 RNA modifications
5'
G
A A A
3'
• RNA methylation (e.g., METTL3, DNMT2)

FIGURE 3-5. Epigenetic mechanisms.

See Plate 23 to view this figure in color.

This figure summarizes the different types of epigenetic modifications. **(1)** DNA modifications: Cytosines can be modified by methylation, hydroxymethylation, formylation, and carboxylation, whereas adenines can only be modified by methylation (adenylation). **(2)** Chromatin modifications: Nucleosomes, composed of DNA wrapped around histone proteins, can change position to increase or decrease DNA accessibility. Nucleosomes also can be modified by adding histone variants and posttranslational modifications. **(3)** Noncoding RNAs can regulate transcription and thus are also considered an epigenetic mechanism. **(4)** RNA modifications (epitranscriptomics): Gene expression can be influenced by RNA modifications, which are also reversible. DNMT2 = DNA methyltransferase-like protein 2; METTL3 = methyltransferase-like 3.

Source. Created with BioRender.com.

Mapping genes to pathways.

Once sets of genes are mapped for a given genome-wide association study, they can be explored using gene network co-expression analyses (Gandal *et al.* 2018) and tested for enrichment in known pathways.

Pathway analysis increases the power of the data because association signals are grouped by functionally related genes. Pathway analysis can provide insight into the cellular-or molecular-level pathways underlying the disorder. Gene Ontology (GO; http://geneontology.org), for example, is a publicly available online resource providing classification of gene function. There are three main categories of terms in GO: Molecular Function, Biological Process, and Cellular Component. A set of terms and their definitions and any defined relationships are set into a hierarchical structure. Each gene is described by multiple GO terms. Beyond identifying functional roles (GO terms) of gene products, *gene ontology enrichment analysis* can be used to statistically determine which terms appear more frequently than expected by chance alone. Such pathway analyses have revealed the relevance of regulation of synapse function, immune function, and also epigenetic factors in psychiatric disease (Network & Pathway Analysis Subgroup of Psychiatric Genomics 2015).

Mapping SNPs to regulatory elements. Mapping causal SNPs from GWAS is complicated by the fact that most association signals for complex disorders, including psychiatric disorders, map to gene regulatory regions, often also at a greater distance from the regulated transcripts. Gene regulatory regions are defined in their activity by epigenetic modifications that alter chromatin accessibility: these include DNA methylation as well as histone modifications (see also Figure 3-5).

DNA methylation (DNAm) regulates gene expression through direct modifications to the DNA. Nucleotides located primarily, but not exclusively, in sequences of cytosine-phosphate-guanine (CpG) dinucleotides are covalently modified (Xie *et al.* 2012). Non-CpG methylation seems to be restricted to specific cell types, such as pluripotent stem cells, and also neurons and glial cells (Jang *et al.* 2017). Increased DNAm is associated with a less accessible DNA sequence, and when this occurs in the promoter region of a gene, it is associated with decreased gene expression. Additionally, hydroxymethyl groups and other chemical DNA modifications (formyl or carboxyl groups) have been described, of which hydroxymethylation occurs preferentially in neurons (Cholewa-Waclaw *et al.* 2016; Traube and Carell 2017). Hydroxymethylation has been associated with facilitating gene transcription.

Histones are an important component of the epigenome, responsible for packaging DNA in chromatin. Histone phosphorylation, acetylation, or methylation at specific amino acid residues regulates how accessible the DNA is (i.e., how tightly or loosely wrapped the DNA is) and thus impacts gene transcription (Hsieh and Gage 2005). The addition or removal of these posttranslational changes is mediated by a number of enzymes, which include histone acetyltransferases as well as histone deactylases. Depending on the chemical reaction, these changes can either promote or inhibit gene transcription.

Using genomic datasets from ENCODE (Encyclopedia of DNA elements) (ENCODE Project Consortium 2012) and its brain-specific counterpart PsychENCODE, as well as Roadmap Epigenomics (Kundaje *et al.* 2015), one can map single SNP loci to putative enhancer elements (see Figure 3-3B, panels 2-4) that are defined by overlaying information on chromatin accessibility (e.g., using assay for transposase-accessible chromatin with sequencing [ATAC-seq]), DNA methylation, and different histone modifications that are assessed using Chromatin ImmunoPrecipitation DNA-Sequencing (Chip-seq). SNPs located within such regulatory elements are enriched among GWAS signals and more likely to be functional, and can impact gene regulation. It should be noted that gene regulatory elements can be specific not only to cell types but also to context, so that mapping in a tissue-and cell-type-specific way as well as under certain stimulation conditions (e.g., immune stimuli) will be important.

Following the mapping of SNPs to regulatory elements and genes, the next step is to infer causality, which can be done through the following processes:

1. Recent technological advances now make it possible to test for allele-specific effects of SNPs on enhancers. Massively parallel reporter assays (MPRAs) evolved from simple *reporter assays* (where a specific regulatory element is cloned into a plasmid upstream of a reporter gene, then transfected into a cell to understand the transcriptional effects of the regulatory element) (see Figure 3-3C, panel 1). The MPRA is a scaled-up version that allows many (tens of thousands) functional regulatory elements to be investigated simultaneously for each allele. These assays allow us to test for regulatory activity in a cell-type and context-specific way. For a review of the applicability of MPRA to psychiatry, see Mulvey *et al.* (2021).
2. Once specific putatively causal SNPs are identified, their effects need to be tested in a cellular context (see Figure 3-3C, panel 2). For this, the combination of CRISPR (clustered regularly interspaced short palindromic repeats)-Cas9 (CRISPR-associated protein 9) technology (which allows us to edit gene sequencing to either introduce or revert a specific genetic variant) and human induced pluripotent stem cells (hiPSCs) has opened up unprecedented possibilities. hiPSCs with specific genetic edits can then be differentiated into either three-dimensional cerebral organoids or two-dimensional brain cells, including neurons and glia, to test for the effects of the genetic variants on cell function. For this, many tools--ranging from omics over imaging to electrophysiology--are available. It is also possible to start to model the effects of multiple variants in an aggregated manner, more closely mimicking the polygenic effects observed in complex diseases (Schrode *et al.* 2019).
3. Although the advent of hiPSC-derived systems now allows us to investigate the effects of genetic variation, including patient-specific variations, on human brain

cell function, the systems are often immature. These investigations can only serve as add-ons to experiments conducted in behaving organisms. Through the use of CRISPR-based models and other tools, laboratory animals carrying human genetic variations can be generated and observed on many levels, including complex behaviors. Finally, hiPSC-derived cells can be transplanted into laboratory animals to study their function in the context of an intact brain (see Figure 3-3C, panel 3).

Gene-by-Environment Interplay

This final section introduces the environment as an important risk factor in interplay with genetic risk and also introduces epigenetics as one mechanism that could mediate gene-by-environment interplay. Trauma, chronic stress, and exposure to adverse life events are the most significant risk factors for many psychiatric disorders (Teicher *et al.* 2022). In fact, adverse life events or traumatic experiences substantially increase risk for MDD, PTSD, substance and alcohol use disorders, bipolar disorder, schizophrenia, and other disorders (Teicher and Samson 2013). Despite their importance in contributing to disease risk and disease presentation, we still have insufficient knowledge about the precise risk mechanisms, thereby limiting therapeutic approaches targeting the consequences of exposure to adversity. We know that not all exposed individuals will develop disease, suggesting underlying individual factors that moderate the relationship between exposure and disease (Elbau *et al.* 2019). Additional exposures to environmental protective or risk factors and timing and duration of the exposures, as well as genetic factors, have been hypothesized to moderate this relationship. Indeed, studies using SNP-based heritability measures suggest a genetic component that may be specific to adversity-associated psychiatric risk. In the U.K. Biobank cohort, an SNP-based heritability of 12% is evident for MDD alone and increases to 24% in patients with reported trauma (Coleman *et al.* 2020). Another study in an independent cohort demonstrates context-specific heritability for different complex traits, including gene-by-adversity effects in depression (Dahl *et al.* 2020).

Identifying the specific variants moderating the effects of adversity has proven difficult, and the investigation of such interactions at the candidate gene, genome-wide, and polygenic levels has yielded inconsistent results

(Border *et al.* 2019; Vassos *et al.* 2022). It is unclear how well such adversity-moderating genetic components could be uncovered from genome-wide interaction studies or other approaches using large cohorts. These approaches are complicated by the requirement of even larger sample sizes, as the complexities of comprehensive adversity definition and characterization (exposome) will increase heterogeneity.

A mechanism that might support the molecular embedding of gene-by-environment interactions is epigenetics (see, e.g., Aristizabal *et al.* 2020 and Klengel and Binder 2015 for reviews). *Epigenetics* refers to processes affecting gene expression and translation that do not involve changes in the DNA sequence and include DNA and RNA modifications and noncoding RNAs (ncRNAs), as well as histone modifications (see Figure 3-5). DNA methylation and histone modifications have been described above in the context of regulatory elements.

ncRNAs play a role in regulating mRNA. Long ncRNAs regulate gene expression by modifying the structure and thus stability of chromatin. Short interfering RNAs (siRNAs) mediate posttranscriptional gene silencing via RNA degradation. Micro-RNAs (miRNAs) fine-tune gene expression by targeting mRNA. miRNAs enforce their effect through direct binding to the 3' untranslated region (3'UTR) of the mRNA of their target gene, leading to an impairment of the synthesis of the encoded protein and faster degradation of the mRNA (Filipowicz *et al.* 2008; Issler and Chen 2015).

The epitranscriptome describes epigenetic changes affecting RNA. It represents another layer of epigenetic regulation that influences many aspects of RNA function, including maturation, stability, distribution, and protein translation. RNA modifications have been documented on almost all types of RNA (Boccaletto *et al.* 2018). The most common and best described RNA modification is the methylation of adenosine on mRNA to N^6-methyladenosine (Yue *et al.* 2015).

Epigenetic mechanisms are influenced by genetic (see subsection "Mapping an Association Signal to Molecular Quantitative Trait Loci" earlier in this chapter) and environmental factors (Aristizabal *et al.* 2020) and are important mechanisms for the integration of genetic and environmental risk factors to lead to changes in gene regulation. Both genetic and environmental factors can drive epigenetic processes, and these factors are not independent and have been shown to interact. Gene-by-environment interactions represent the influence of environmental and genetic factors on a measured phenotype--in this case, epigenetic modifications. In two studies of newborns (Czamara *et al.* 2019; Teh *et al.* 2014), the influence of the prenatal environment and genotype on genome-wide DNA methylation was examined and revealed combined effects of genotype and environment. Additive and multiplicative effects explained a much larger proportion of DNA methylation variation than did genotype or environment alone, supporting the importance of considering genotype in epigenetic studies.

Conclusion

In as early as 2005, Kendler pointed out that the phrase "a gene for . . ." will not apply to psychiatric genetics, noting that "the impact of individual genes on risk for psychiatric illness is small, often nonspecific, and embedded in a complex causal pathway" (Kendler 2005, p. 1243). Indeed, psychiatric disorders are polygenic in nature, with numerous genes individually contributing a small impact on risk. Today, there is little dispute as to the important role genetics plays in psychiatric disorders. As such it holds the strongest promise for uncovering the underlying pathomechanisms.

There still remain many challenges in genomics within psychiatry. Although genetic testing is recommended in patients with ASD or intellectual developmental disorder, in reality, its clinical use is still very limited. Specific guidance on genetic testing and clinical pharmacogenetics can be found in the recommendations published in a statement by the International Society of Psychiatric Genetics (2019). However, despite pharmacogenomic testing (and guidelines for its use) being widely available, its utility has not yet been clearly established. One final goal for the use of genomics in psychiatry is to deliver personalized medicine (Figure 3-6). Given the likely future impact this field will have on clinical care, it can be argued that the education of genetic principles in psychiatry should be at the forefront of training. Next-generation sequencing will soon become clinically relevant; therefore, the use of genetic counseling in psychiatry is essential and should become an integral part of psychiatric training (Nurnberger *et al.* 2018).

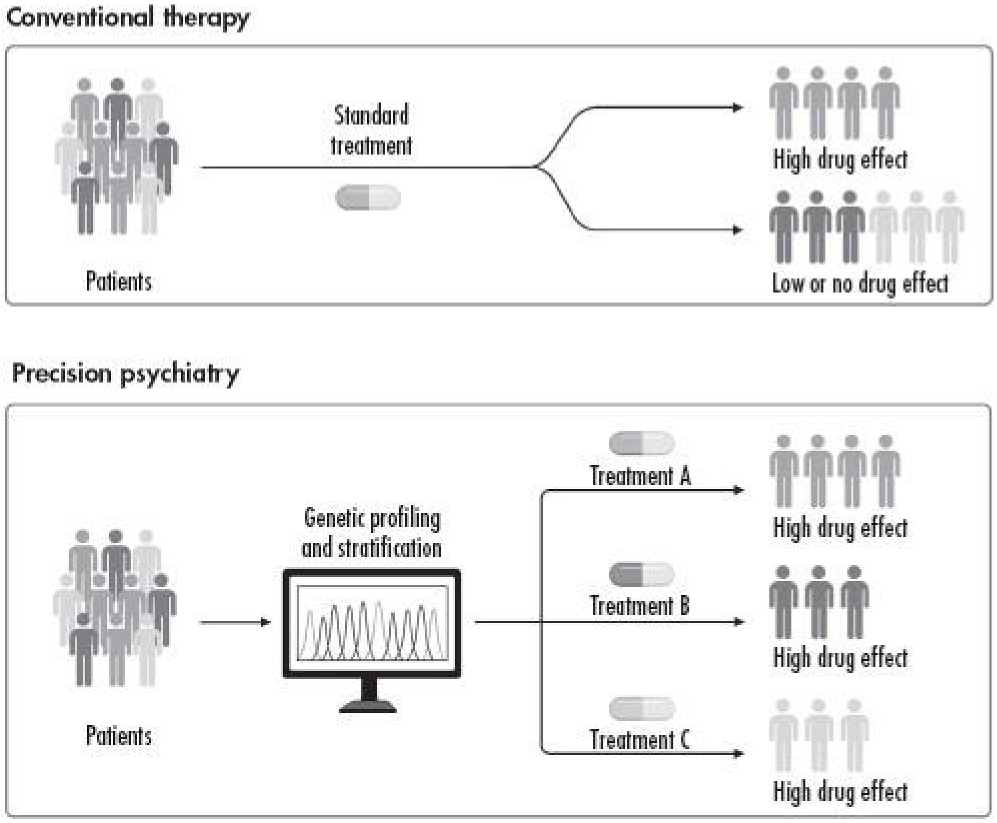
Conventional therapy
Patients
Standard treatment
High drug effect
Low or no drug effect
Precision psychiatry
Patients
Genetic profiling and stratification
Treatment A
Treatment B
Treatment C
High drug effect
High drug effect
High drug effect

FIGURE 3-6. Precision psychiatry.

See Plate 24 to view this figure in color.

Genetic profiling together with other measures may allow patient stratification that can be used to target treatments more efficiently.

Source. Created with BioRender.com.

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CHAPTER 4

Psychoneuroendocrinology

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The neuroendocrine system is the major route of communication between body and mind. It results from the interaction between the endocrine system and the nervous system (Toni 2004). These two systems interact through different chemical signs--hormones for the endocrine system and neurotransmitters for the nervous system--to maintain the homeostasis, that is, the equilibrium between every single component of the body. Given the strong connection between body and mind, an alteration in homeostasis could be both a cause and a consequence of mental illnesses. Psychoneuroendocrinology studies exactly this, the bidirectional connection between the neuroendocrine system and psychiatric symptoms. Growing research has revealed how neuroendocrine dysregulations are frequently associated in a bidirectional link with different psychiatric conditions, including major depressive disorder (MDD) (Belvederi Murri *et al.* 2014), bipolar disorder (Daban *et al.* 2005), psychotic disorders (Rutigliano *et al.* 2020), and trauma-and stress-related disorders (D'Elia *et al.* 2021). In this chapter, we aim to examine the evidence on psychoneuroendocrinology. We first describe the physiology of the neuroendocrine system. We then focus on the role of this system in psychiatric disorders and discuss the clinical relevance of this relationship.

Physiology of the Neuroendocrine System

The neuroendocrine system consists of four major elements: the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), and hypothalamic-pituitary-gonadal (HPG) axes and the hypothalamic-neurohypophyseal system. All the "axes" (HPA, HPT, and HPG) operate in a similar way. The hypothalamus is the coordinating center, with numerous peripheral and central inputs and a major output toward the pituitary gland, or *hypophysis*. Indeed, hypothalamic neurohormones are also called *releasing hormones* because of their ability to regulate the secretion of hormones from the anterior pituitary (or *adenohypophysis*). Finally, pituitary hormones stimulate hormone production in peripheral glands. An important feature of the neuroendocrine system is the negative feedback loop by which each axis self-regulates its own hormone production. Hormones produced at a peripheral level act upstream from the axis, inhibiting the release of the respective hypothalamic and pituitary hormones. The hypothalamic-neurohypophyseal system operates in a slightly different way. Hypothalamic neurons and their axonal projections cause the release of hormones from the posterior pituitary (or *neurohypophysis*) to the bloodstream. Readers interested in a more detailed discussion of the neuroendocrine system and its role in mood disorders are referred to the chapter by Sforzini and colleagues in *The American Psychiatric Association Publishing Textbook of Mood Disorders*, Second Edition (Sforzini *et al.* 2022). Figure 4-1 schematically outlines the physiology of the neuroendocrine system.

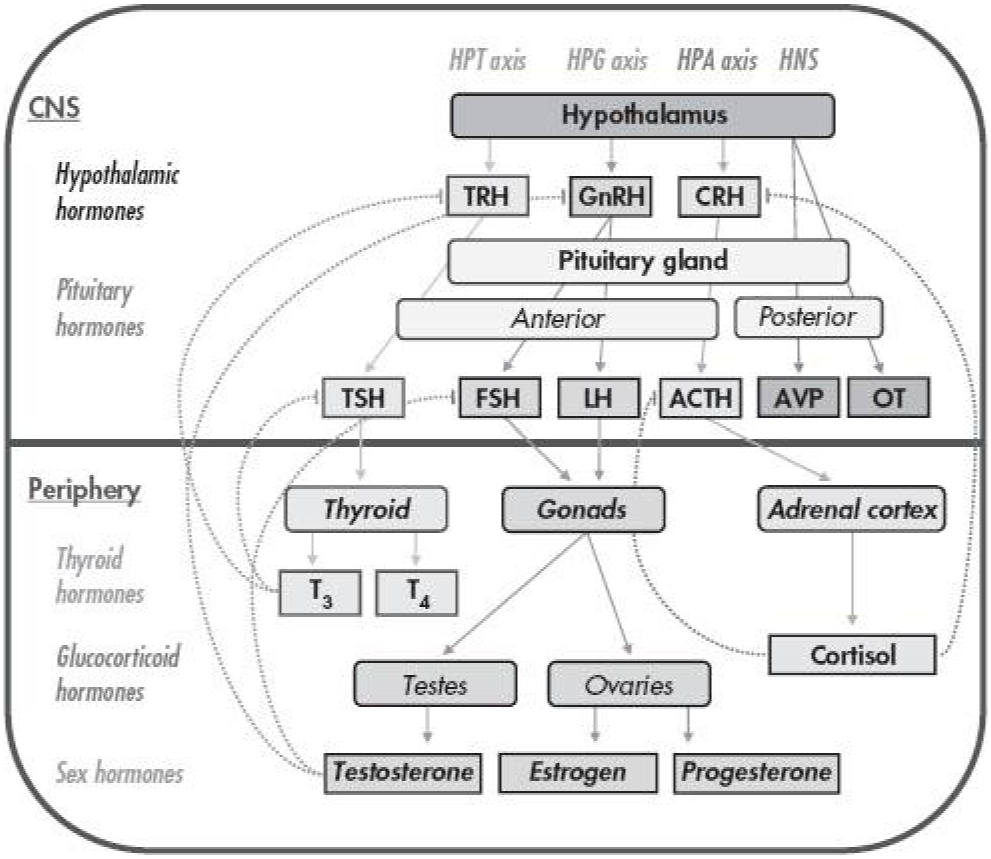
HPT axis
HPG axis
HPA axis
HNS
CNS
Hypothalamus
Hypothalamic hormones
TRH
GnRH
CRH
Pituitary gland
Pituitary hormones
Anterior
Posterior
TSH
FSH
LH
ACTH
AVP
OT
Periphery
Thyroid
Gonads
Adrenal cortex
Thyroid hormones
T_3
T_4
Glucocorticoid hormones
Cortisol
Testes
Ovaries
Sex hormones
Testosterone
Estrogen
Progesterone

FIGURE 4-1. Physiology of the neuroendocrine system.

See Plate 25 to view this figure in color.

Schematic representation of the four major neuroendrocrine elements: the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), and hypothalamic-pituitary-gonadal (HPG) axes and the hypothalamic-neurohypophyseal system (HNS). Hypothalamic neurons produce releasing hormones and HNS hormones. Releasing hormones act on the anterior pituitary gland, causing the release of stimulating hormones. HNS hormones are released from hypothalamic axons in the posterior pituitary, or neurohypophysis. The stimulating hormones produced in the pituitary gland stimulate peripheral organs (thyroid, gonads, and adrenal cortex) to produce specific hormones, which in turn exert several biological functions (T_3, T_4; testosterone, progesterone, estrogens; and cortisol, respectively). These peripheral hormones can act backwards within each axis, self-controlling their production in a negative feedback loop. The HPT axis is represented in *yellow*; the HPG in *red*; the HPA in *green*; the hypothalamus and HNS in *blue*; and the pituitary gland in *light blue*. *Arrows* indicate stimulation, and *dotted lines* indicate inhibition. Hormone-producing organs are described in *rounded boxes*, and hormonal products are depicted as *rectangles*. ACTH = adrenocorticotropic hormone; AVP = arginine vasopressin; CNS = central nervous system; CRH = corticotropin-releasing hormone; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; OT = oxytocin; T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

Source. Reprinted from Figure 6-1 (p. 107) in Sforzini L, Nettis MA, Weston FI, Pariante CM: "Psychoneuroendocrinology of Mood Disorders," in The American Psychiatric Association Textbook of Mood Disorders, 2nd Edition. Edited by Nemeroff CB, Rasgon N, Schatzberg AF, Strakowski SM. Washington, DC, American Psychiatric Association Publishing, 2022, pp. 105-131. Copyright (c) 2022, American Psychiatric Association. Used with permission.

Hypothalamic-Pituitary-Adrenal Axis

The HPA axis is a key immune modulator and the main component of the stress response, together with the autonomic nervous system (ANS) (Ulrich-Lai and Herman 2009). In response to stressful and potentially harmful stimuli, our body reacts with multifaceted biological effects intended to promote the fight-or-flight response. The ANS represents the most rapid response, while the HPA axis is responsible for more complex and both acute and longer-term biological modifications, modulating homeostasis in the whole body.

Neurons of the paraventricular nucleus (PVN) of the hypothalamus produce corticotropin-releasing hormone (CRH), leading to the release of adrenocorticotropic hormone (ACTH) in the anterior pituitary. ACTH stimulates the cortical region of the adrenal glands, which are two endocrine glands located on top of the kidneys. The final products of the HPA axis are glucocorticoid hormones, mainly cortisol in humans (see Figure 4-1). Glucocorticoids are steroid hormones, synthesized from cholesterol, that are capable of passing through cells' lipidic membranes and acting on nuclear receptors. Cortisol levels change in accord with the circadian rhythm. They reach their highest levels in the morning shortly after awakening (usually around 8 A.M.), in what is known as the *cortisol awakening response* (CAR) (Elder *et al.* 2014); they then progressively decline, reaching the lowest level during the night, about 3-5 hours after falling asleep (roughly from midnight to 4 A.M.).

There are two different types of receptors for glucocorticoids: glucocorticoid receptors (GR), encoded by *NR3C1* (the nuclear receptor subfamily 3, group C, member 1 gene), and mineralocorticoid receptors (MR). Cortisol binds to GR with low affinity and to MR with high affinity.

This finding supports the hypothesis that MR binding is mainly involved in the homeostatic basal function, whereas cortisol-GR binding is more clearly related to stress response, when cortisol levels are increased (Pariante 2004). GR is therefore the main modulator of HPA axis activity. It is necessary for life after birth and is expressed in nearly every cell of the body. Following glucocorticoid binding, GR regulates the transcription of target genes and mediates composite biological actions (Oakley and Cidlowski 2013). The gene *FKBP5*, encoding FK506-binding protein 51 (FKBP51), a co-chaperone protein, is central in GR functioning and sensitivity (Alhajji and Nemeroff 2015). FKBP51 physiologically binds to the GR complex, reducing the receptor affinity for glucocorticoid. Following the activation of GR by glucocorticoids, transcription and translation of *FKBP5* are increased, and this reduces the GR sensitivity in an ultra-short negative feedback loop (Binder 2009; Menke 2019).

The production of glucocorticoids is finely regulated. Similar to what we will discuss for other components of the neuroendocrine system, under physiological conditions cortisol inhibits the synthesis of CRH/ACTH by exerting negative feedback (see Figure 4-1) (Zunszain *et al.* 2013). Notably, GR mediates this negative feedback. Thus, when GR is disrupted, such as in chronic glucocorticoid stimulation, the negative feedback is impaired. This phenomenon is called *glucocorticoid resistance* and in turn leads to HPA axis hyperactivity (Pariante and Lightman 2008; Pariante and Miller 2001). Suppression tests evaluate the efficacy of the negative feedback mechanism. They are the most diffused clinical tests to evaluate the HPA axis. Cortisol levels are measured after the injection of exogenous steroids, such as dexamethasone, which binds to GR, in the dexamethasone suppression test, and prednisolone, which probes both GR and MR (Juruena *et al.* 2009), in the prednisolone suppression test.

Hypothalamic-Pituitary-Thyroid Axis

The HPT axis is crucial in regulating metabolism, influencing basal metabolic rate, energy balance, protein synthesis, and cell growth. The hypothalamic thyrotropin-releasing hormone (TRH) stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH). TSH induces the thyroid, an endocrine gland located in the anterior part of the neck, to produce the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4), together with the peptide hormone calcitonin (see Figure 4-1). T_4 is mainly released into the bloodstream and then enzymatically converted to T_3. T_3 has much higher affinity for the thyroid hormone nuclear receptor (TR) (Baek *et al.* 2014). Under pathological conditions, thyroid functioning could be increased (hyperthyroidism) or reduced (hypothyroidism). In addition, TSH levels may be altered (increased or reduced) in the presence of normal levels of thyroid hormones (subclinical hyperand hypothyroidism, respectively). As described for the HPA axis, T_3 and T_4 inhibit TRH and TSH secretion via negative feedback (see Figure 4-1).

Hypothalamic-Pituitary-Gonadal Axis

The HPG axis is the principal modulator of the reproductive system. The hypothalamic gonadotropin-releasing hormone (GnRH) stimulates the anterior pituitary to produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (see Figure 4-1). These two hormones act on the gonads with different and precise functions. In females, they promote the ovarian production of estrogen and progesterone, regulating menstrual and ovarian cycles. In males, they chiefly induce the testicular production of testosterone, regulating spermatogenesis. Again, sex hormones could inhibit their own production by acting on the hypothalamus or hypophysis in a negative feedback loop (see Figure 4-1). Estrogens and testosterone are largely bound to carrier proteins, mainly albumin and sex hormone-binding globulin, and only in a very small percentage (approximately 1%-2%) they are unbound--so-called free--

and bioactive. Remarkably, estrogens widely change their levels in relation to life stages and menstrual and ovarian cycles. Testosterone levels can vary, even if less intensely, according to one individual's age. Notably, though, androgen levels may also vary within the same day, similarly to cortisol levels, with significant diurnal variation (Long *et al.* 2015). Sex hormones act on specific nuclear receptors. There are two main types of estrogen receptors, alpha (ER-a) and beta (ER-b) receptors, and one androgen receptor. The progesterone receptor has two main isoforms (PR-A and PR-B), which differ in molecular weight (Jacobsen and Horwitz 2012). Sex hormone receptors are nuclear, similar to GR, MR, and TR.

Notably, there is a mutual connection between the HPG and HPA axes. Increased glucocorticoid levels inhibit GnRH and gonadotropins levels, while sex hormones regulate levels of cortisol (Toufexis *et al.* 2014). As an example, Cushing's syndrome is frequently associated with amenorrhea (Zada *et al.* 2015). In addition, HPA axis hypoactivity may result in chronically high testosterone levels (Ludwig *et al.* 2019).

Hypothalamic-Neurohypophyseal System

The hypothalamic-neurohypophyseal system involves the posterior pituitary, or neurohypophysis. This system is different from systems in the anterior pituitary, because it does not produce hormones directly, but instead includes axonal projections of hypothalamic neurons. Hypothalamic neurons produce two structurally related hormones, oxytocin and vasopressin (or arginine vasopressin, AVP), which are then released into the neurohypophyseal capillaries and from there into the bloodstream (see Figure 4-1). Oxytocin facilitates parturition and lactation by acting on uterus smooth muscles and mammalian glands. Interestingly, it additionally plays a significant role in social functioning (Jones *et al.* 2017), where it promotes affiliation and both mother-child and pair bonding and modulates fear and anxiety behavior (Zik and Roberts 2015). AVP regulates body water balance and fluid homeostasis and chiefly regulates blood pressure, osmotic balance, and kidney function. Therefore, it is also called *antidiuretic hormone* (ADH). Under pathological conditions, the release of AVP can be increased, as is observed in the syndrome of inappropriate ADH secretion (SIADH), or decreased, causing diabetes insipidus (Verbalis 2014). AVP acts on three different receptors: V_{1a}, V_{1b} (also known as V_3), and V_2 (Surget and Belzung 2008). On the other hand, oxytocin has a unique receptor. Notably, oxytocin and AVP and their receptors show high homology, potentially accounting for signaling crosstalk (Rae *et al.* 2022). Also, both neurohypophyseal hormones can affect the HPA axis activity (Engelmann *et al.* 2004). Particularly, AVP is a main regulator of the HPA axis. It modulates the secretion of ACTH and is possibly involved in HPA hyperactivation--mainly through the V_{1b} receptor--under stress conditions (Goncharova 2013).

Immune-Neuroendocrine Interactions

The immune system and its response, inflammation, are strongly connected to both the neuroendocrine system and psychiatric disorders. They are, therefore, important factors in the relationship we are debating in this chapter. Inflammation has been consistently associated with the pathophysiology of several psychiatric diseases, including mood (Pariante 2017; Stetler and Miller 2011), psychotic (Kose *et al.* 2021), and stress-related disorders (Heim 2020; Sumner *et al.* 2020). In addition, compelling evidence has demonstrated complex immune-neuroendocrine crosstalk (Ashley and Demas 2017). Immune cells can produce low levels of different hormones, and neuroendocrine cells can release inflammatory cytokines (Verburg-van Kemenade *et al.* 2017). In this section, we briefly discuss the main interactions between the neuroendocrine system and the immune processes.

The HPA axis is the most important component in immune-neuroendocrine interactions, being strongly and bidirectionally connected with the immune system. It modulates the inflammatory responses that occur throughout the whole body, including the CNS (Otmishi *et al.* 2008). Cortisol has an extremely powerful anti-inflammatory effect and can be activated by several proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-a). In addition, immune cells express both GR and adrenergic receptors (Menard *et al.* 2017). Hyperactivation of the HPA axis, which is typical of chronic stress conditions (such as chronic illnesses), can induce persistent glucocorticoid resistance. The related absence of GR-mediated negative feedback leads to HPA axis hyperactivity, and, at the same time, the absence of GR-mediated restraint of inflammation leads to increased inflammation (Pariante 2014). In a recent meta-analysis testing the association between glucocorticoid resistance and increased inflammation in depression, Cattaneo *et al.* (2020) found limited evidence for a positive association between glucocorticoid resistance and inflammation. In addition, despite the presence of increased inflammatory biomarkers and reduced GR messenger RNA (mRNA) expression in the MDD patients analyzed, the Biomarkers in Depression (BIODEP) study similarly found unclear evidence for a correlation between inflammatory biomarkers, GR mRNA expression, and salivary cortisol levels (Cattaneo *et al.* 2020). Therefore, the "glucocorticoid resistance model" may not be the only one explaining the complex relationship between glucocorticoid resistance and inflammation, suggesting a need for further research (Perrin *et al.* 2019).

Glucocorticoids may also have proinflammatory properties. Horowitz *et al.* (2020) showed that the administration of dexamethasone before an immune challenge enhanced the inflammation in human hippocampal progenitor cells in vitro and upregulated multiple innate immune genes. Therefore, there is also evidence of an altered glucocorticoid resistance model, in which cortisol acts as a proinflammatory mediator. An excess of cortisol may also stimulate the inflammation-related kynurenine pathway (Menke 2019). This pathway is activated during inflammation and in several psychiatric conditions, including depression (Sforzini *et al.* 2019) and schizophrenia (Kindler *et al.* 2020). Therefore, it has been proposed as a potential biological shared mechanism for psychiatric disorders comorbid with immune-related diseases.

The immune system is related to the HPT axis as well (Masek *et al.* 2003). Thyroid is essential to the normal development of the thymus, a specialized organ of the immune system. Here, thymocytes, which are hematopoietic precursors from bone marrow, mature into T-lymphocytes. This relationship is again bidirectional; activated immune cells can synthesize and secrete small quantities of TRH (Masek *et al.* 2003). In addition, the thyroid is an organ often affected by autoimmune disorders

(McLeod and Cooper 2012). Autoimmunity is a process by which an individual's immune system is activated against its own healthy components. In the thyroid, three different proteins can be targeted by three specific autoantibodies, which are directed against thyroid peroxidase, thyroglobulin, and TSH receptors. Autoimmune thyroiditis can cause both hyperand hypothyroidism, depending on the target and the stage of the illness.

The HPG axis and the hypothalamic-neurohypophyseal system have a similar and bidirectional link with the immune system. Immune cells express both estrogen (ER-a and ER-b) and androgen receptors (Taub 2008). Also, inflammatory cytokines, such as IL-1, can stimulate the release of both AVP and oxytocin (Landgraf *et al.* 1995).

Role of the Neuroendocrine System in Psychiatric Disorders

Under physiological conditions, our body and mind can face even massive perturbations and maintain homeostasis. An appropriate response to stress requires effective neuroendocrine and immune systems (McEwen *et al.* 2015; Ulrich-Lai and Herman 2009). Disruptions at any level within the neuroendocrine system could result in severe consequences for the individual's health, including mental health; conversely, the neuroendocrine system may be altered as a consequence of different psychiatric diseases (Van Dammen 2021). We now discuss the main interconnections between the neuroendocrine system and different mental disorders, categorized, following the DSM-5 classification (American Psychiatric Association 2013), as "depressive disorders," "bipolar and related disorders," "schizophrenia spectrum and other psychotic disorders," and "trauma-and stressor-related disorders."

Depressive Disorders

HPA Axis

The HPA axis mediates between stress responses and brain functioning (Pariante and Lightman 2008) and is highly interconnected with depressive disorders. Indeed, HPA axis hyperactivity is probably the most prominent and consistent neuroendocrine abnormality found in depression (Min *et al.* 2012; Pariante and Lightman 2008). HPA hyperactivity has also been proposed as a factor in the high prevalence of comorbid medical illnesses during depression (Stetler and Miller 2011). In addition, depressed patients frequently have altered responses to the dexamethasone suppression test and reduced GR mRNA expression (Palazidou 2012). A large meta-analysis confirmed this evidence of HPA axis hyperactivity in depressed individuals (Stetler and Miller 2011). The authors demonstrated that depressed individuals had significantly increased levels of cortisol (54 studies on 18,374 individuals) and ACTH (96 studies on 3,812 individuals) compared with healthy subjects. On the other hand, CRH levels were not significantly different and tended to be higher in the depressed group only when assessed in blood, but lower when assessed in CSF. Even though these effects were not significant, they may suggest a different physiological meaning of CRH levels in blood and CSF.

The degree of HPA hyperactivity varied across depression phenotypes, being the most marked in older hospitalized individuals and in depression with melancholic or psychotic features (Stetler and Miller 2011). So, notably, clinical features such as depression specifiers or age could influence HPA abnormalities. A recent study confirmed

increased cortisol levels in patients with depression with psychotic features compared with healthy subjects and with patients with nonpsychotic depression (Cherian *et al.* 2019). Moreover, Lamers *et al.* (2013) confirmed that specifiers of depression may be associated with different biological correlates. They observed that subjects with depression with melancholic features had a hyperactive HPA axis compared with control subjects. On the other hand, patients with atypical features presented a lower diurnal slope compared with control subjects and subjects with melancholic depression

(Lamers *et al.* 2013). In a recent systematic review, Agustini *et al.* (2019) analyzed patients with depression with a seasonal pattern. They found attenuated CAR during winter--but not in summer--in these patients compared with healthy control subjects, even though evidence on this specifier is still scarce. In their meta-analysis, Belvederi Murri *et al.* (2014) found significantly higher cortisol levels in elderly depressed patients (older than 60 years) compared with healthy control subjects, and this effect was even higher when postdexamethasone cortisol levels were analyzed. As the authors suggested, these higher levels could be due to different mechanisms related to aging and thus not directly related to depression.

Sex also may contribute to HPA dysfunction in depression. As an example, Sanches *et al.* (2013) found significantly higher cortisol levels in depressed patients compared with healthy control subjects, but only in males. However, evidence to date is still inconclusive. Women in the perinatal period, including both pregnancy and the postpartum period, are at higher risk of developing depression (Sawyer *et al.* 2019). The HPA axis is typically hyperactivated during physiological pregnancy. The placenta produces CRH, GR function is reduced, and glucocorticoid resistance develops (Glynn *et al.* 2013). Notably, these alterations are enhanced when depressive symptoms co-occur (Katz *et al.* 2012; Pariante 2014). During the postpartum period, CRH levels drop, with subsequent decreases in ACTH and cortisol levels. This HPA "refractory period" is a vulnerable period for the development of depression and may persist for weeks, months, or even years (Dickens and Pawluski 2018; Glynn *et al.* 2013). Furthermore, depression during pregnancy is associated with increased cortisol response to stress in offspring at 1 year of age (Osborne *et al.* 2018).

HPA alterations may mediate and predict the development of depression, being a risk factor for depression and not simply a consequence or epiphenomenon of it (Pariante and Lightman 2008). Hardeveld *et al.* (2014) demonstrated that increased CAR was associated with time to recurrence of depression and not dependent on stress-related factors. In contrast, Tsuru *et al.* (2013) analyzed patients hospitalized for depression and found no correlation between baseline HPA markers (combined dexamethasone/CRH levels) and recurrence of depressive symptoms within 10 years. HPA alterations could also predict response to antidepressant treatments. In a placebo-controlled study examining HPA axis response to a prednisolone suppression test administered to individuals with severe depression prior to receiving intensive multimodal inpatient treatment, Juruena *et al.* (2009) found higher cortisol levels and a lower percentage of suppression in patients who were subsequent nonresponders to inpatient treatment compared with those who were responders.

Finally, the HPA axis can also be chronically activated by early-life stress, including childhood maltreatment (Cousins and Goodyer 2015). This sustained hyperactivation may be an independent factor predisposing to the development of depression during adolescence and adulthood (Cousins and Goodyer 2015; Pariante and Lightman 2008; van Bodegom *et al.* 2017). Notably, the GR gene is susceptible to epigenetic modification, specifically DNA methylation (Smart *et al.* 2015). Additionally, Normann and Buttenschon (2020) have found significant HPA axis gene-environment interactions between *CRHR1*, *FKBP5*, *NR3C1*, *NR3C2,* and childhood maltreatment. Early life adversity may also influence the HPA axis during pregnancy, with greater CAR, and moderate the effect of depression on diurnal slope (Epstein *et al.* 2020).

Also crucial in the relationship is the GR complex, particularly the gene *FKBP5*. Different *FKBP5* single-nucleotide polymorphisms (SNPs) (rs1360780, rs3800373, rs4713916, rs9296158, rs9394309, rs9470080) have been significantly associated with MDD (Lekman *et al.* 2008; Szczepankiewicz *et al.* 2014) and with an increased recurrence of depressive episodes (Binder *et al.* 2004). In addition, significantly higher *FKBP5* mRNA levels have been reported in MDD patients compared with control subjects (Cattaneo *et al.* 2013) and are seen in both the hippocampus (Mamdani *et al.* 2015) and the frontal cortex (Tatro *et al.* 2009). This evidence suggests that certain GR complex polymorphisms may cause a baseline difference in GR sensitivity, increasing GR resistance and decreasing efficiency of negative feedback on the HPA axis, thereby increasing MDD risk. Notably, *FKBP5* SNPs (e.g., rs1360780) have also been associated with antidepressant response, remission, and resistance (Fabbri *et al.* 2018; Stamm *et al.* 2015). These variations may explain why HPA axis dysregulation has been seen prior to a depressive episode and can predict development of depressive symptoms or the response to treatments. Interestingly, gene-environment interactions have also been implicated in GR alterations in MDD. In a study evaluating *FKBP5* polymorphisms (rs3800373, rs9296158, rs1360780, rs9470080) in preschool children, minor allele carriers of the SNPs had significantly increased risk of developing MDD if exposed to adverse life events compared with homozygous carriers of the major allele (Scheuer *et al.* 2016). This increased risk was observed only in individuals exposed to mild to moderate adverse events, rather than severe. Further research corroborated these findings, showing that adolescent carriers of *FKBP5* SNPs (rs3800373, rs1360780) who had also undergone moderate early-life stress had increased risk of MDD (Piechaczek *et al.* 2019). An increased risk of MDD is also present in adolescent carriers of *FKBP5* SNPs (rs3800373, rs9296158, rs9470080) who have undergone sociodemographic stress. Kang *et al.* (2020) reported significant interaction effects between *FKBP5* SNPs (rs3800373, rs1360780, rs4713916) and childhood physical abuse. Individuals with the minor alleles of the SNPs showed higher depression scores compared with noncarriers when exposed to abuse. It is important to remark that these SNPs alone had no significant effect on the risk of MDD, because exposure to early-life stress was crucial (Kang *et al.* 2020; Piechaczek *et al.* 2019). Therefore, minor alleles of the *FKBP5* polymorphisms act as risk alleles, increasing susceptibility to the pathogenic effects of environmental factors, such as childhood abuse, on the development of MDD.

HPT Axis

HPT axis abnormalities are frequent in depressive disorders (Fountoulakis *et al.* 2006; Nemeroff and Evans 1989). The HPT axis generally appears to be hypoactive (Swaab *et al.* 2005) and may be disrupted at different levels. Alterations can be both central (hypothalamic and pituitary), with reduced TSH secretion (Duval *et al.* 2021) and increased TRH activity, and peripheral (in the thyroid), with elevated T_4 levels, low T_3 levels, and positive antithyroid autoantibodies (Hage and Azar 2012).

Serotonin is critical in HPT axis regulation, mainly inhibiting TRH secretion. Hence, the serotonin depletion typical of depression may be linked with increased secretion of TRH and blunted TSH response (Duval *et al.* 2002). However, most individuals with depression have no overt abnormalities in thyroid function, even though they probably have a greater prevalence of subclinical hypothyroidism compared with the general population (Bauer *et al.* 2008). Notably, Brouwer *et al.* (2005) reported higher TSH levels in depressed outpatients compared with matched control subjects, suggesting an opposite dysregulation of the HPT axis. Interestingly, Tsuru *et al.* (2013) found significantly higher TSH responses to TRH in patients whose depression recurred over a 10-year period after remission.

This relationship is bidirectional, and depression is frequently comorbid with thyroid illnesses. Hypothyroidism is the most consistently related with depression, but there is evidence for hyperthyroidism as well (Bauer *et al.* 2008). In subclinical hypothyroidism, findings are more debated. In their meta-analysis, Zhao *et al.* (2018) noticed this association only in younger patients. On the other hand, Medici *et al.* (2014) found that low TSH levels, but still within the normal range, were related to future development of depression in elderly patients. In a cross-sectional study on MDD patients, Shen *et al.* (2019) found higher serum TSH, anti-thyroglobulin antibodies, and thyroid peroxidase antibodies in individuals who had attempted suicide compared with individuals who had not attempted suicide. Thyroid peroxidase antibodies have been extensively associated with depression, also in specific clinical subgroups such as postnatal depression (Wesseloo *et al.* 2018) and subclinical hypothyroidism (Juceviciute *et al.* 2019). However, some studies did not find associations between thyroid peroxidase antibodies and depression, but did find higher concentrations of TSH receptor antibodies in depressed patients compared with control subjects (Fam *et al.* 2015). Lastly, a preclinical study found that mice with receptor-mediated hypothyroidism--caused by an unliganded TRa_1--presented a depressive phenotype, which was responsive to T_3 substitution (Pilhatsch *et al.* 2010).

HPG Axis

Growing research focuses on the role of sex hormones in mental health (Lombardo *et al.* 2021). Depressive disorders are more prevalent in women, particularly during the reproductive years (Salk *et al.* 2017). Sex hormones may therefore be involved in the pathogenesis of depression. However, a clear correlation has yet to be established (Brummelte and Galea 2016; Hammarstrom *et al.* 2009). Additionally, a recent meta-analysis found a significant association between female depression and higher serum testosterone (absolute standardized mean difference) (Maharjan *et al.* 2021). Estrogens regulate the synthesis, metabolism, receptor concentration, and trafficking of serotonin, dopamine, and norepinephrine, neurotransmitters greatly involved in depression. In addition, they regulate neuroplasticity by altering brain-derived neurotrophic factor (BDNF) levels (Schiller *et al.* 2016). An imbalance in testosterone levels has also been associated with increased risk for depression, in both sexes (Rohr 2002). Lower testosterone levels--mainly free--have been reported in males with depression (Almeida *et al.* 2008). A recent meta-analysis confirmed significantly lower testosterone levels in depressed men compared with control subjects (Fischer *et al.* 2019a). Additionally, depressed men have significantly lower estradiol levels compared with control subjects (Arinami *et al.* 2021).

Clearly, perinatal depression concurs with massive physiological alterations of sex hormones. Estrogen and progesterone levels dramatically rise and fall during pregnancy and postpartum. Both estrogens and androgens during pregnancy are involved in the development of mental changes in the postpartum period (Parizek *et al.* 2014). Furuta *et al.* (2013) demonstrated how an estrogen-mediated mechanism, mainly involving ER-a, may attenuate the onset of depressive-like behaviors in postpartum rats. Guintivano *et al.* (2014) identified epigenetic alterations in estradiol-mediated signaling genes that are implicated in postpartum depression, using combined mouse and human data.

Premenstrual dysphoric disorder (PMDD) is another important clinical condition that may affect women of reproductive age. Women with PMDD may have a higher sensitivity to changes in sex hormones, mainly the fall in progesterone levels, experiencing affective symptoms during the luteal phase of the menstrual cycle (with complete inter-episodic remission). Selective serotonin reuptake inhibitors (SSRIs) are rapidly effective in this disorder, and this may be due to their action on sex hormones, neuromodulating estrogen or progesterone levels (Lanza di Scalea and Pearlstein 2017; Yonkers and Simoni 2018).

Hypothalamic-Neurohypophyseal System

Hypothalamic-neurohypophyseal system hormones have also been studied in depression. AVP has been demonstrated to influence several CNS-related functions, including cognitive and behavioral ones (Surget and Belzung 2008). It has also been hypothesized to have a depressogenic effect. In fact, higher AVP plasma levels (van Londen *et al.* 1998) and increased AVP mRNA expression (Meynen *et al.* 2006) have been reported in depressed patients compared with control subjects. Interestingly, a major SNP haplotype of AVP receptor has been found to be protective against recurrent MDD (van West *et al.* 2004). In addition, AVP stimulates ACTH production synergistically with CRH, thus activating the HPA axis (Salata *et al.* 1988); this has been proposed as a main depressogenic mechanism (Neumann and Landgraf 2012).

Oxytocin may also be involved in the development or maintenance of depression (McQuaid *et al.* 2014). Decreased oxytocin levels have been associated with depression (Lach *et al.* 2018). In addition, perinatal depression has been linked to oxytocin levels, in a reciprocal link: low oxytocin levels during pregnancy are associated with risk of postnatal depression, and antenatal depression is associated with low oxytocin levels after birth (Sawyer *et al.* 2019). Epigenetic studies showed that DNA methylation in the oxytocin receptor gene was associated with postpartum depression (Kimmel *et al.* 2016), and specifically with persistent symptoms (King *et al.* 2017). Oxytocin may differently regulate HPA axis activity by inhibiting basal HPA axis activity and potentiating it under conditions of stress (Neumann *et al.* 2000).

Bipolar and Related Disorders

HPA Axis

Compelling research suggests that bipolar disorders may be associated with hyperactivation of the HPA axis (Daban *et al.* 2005). When bipolar and related disorders are being evaluated, it is necessary to consider that neuroendocrine alterations may differ accordingly to the phase of the disease (manic, major depressive, or mixed episode). These phase-specific alterations complicate research. Subjects with bipolar disorder, in both manic and depressive phases, have a significantly increased ACTH response to the combined dexamethasone/CRH suppression test compared with control subjects (Schmider *et al.* 1995). Also, patients with bipolar disorder whose disorder is in remission have an increased cortisol response to the dexamethasone/CRH test (Watson *et al.* 2004). A comprehensive meta-analysis (Belvederi Murri *et al.* 2016) endorsed these findings. Subjects with bipolar disorder displayed significantly higher ACTH and cortisol levels at awakening, and, similarly, when measured over 12 or 24 hours, compared with control subjects (Belvederi Murri *et al.* 2016). van den Berg *et al.* (2020) found elevated hair cortisol concentration in bipolar disorder patients compared with control subjects, with a significant peak in hair cortisol in the months prior to a manic episode. Feng *et al.* (2019) measured neuroendocrine function in untreated newly diagnosed patients with MDD and with bipolar disorder. The authors demonstrated a hyperactive HPA axis (higher ACTH and cortisol levels) in patients with MDD compared with those with bipolar disorder. These findings corroborate a potential difference between unipolar and bipolar depression, as well as a difference in neuroendocrine functioning. From a clinical point of view, both melancholic and atypical symptoms are common in bipolar depression (Belvederi Murri *et al.* 2016). As discussed, these specifiers correlate with opposing biological HPA effects (Lamers *et al.* 2013).

GR is a crucial mediator of this relationship. Research demonstrated decreased levels of GR protein (Bei *et al.* 2009), or GR-a mRNA (Matsubara *et al.* 2006), in subjects with bipolar disorder. Decreased GR-a mRNA was also identified in healthy first-degree relatives of patients with bipolar disorder (Matsubara *et al.* 2006). GR alterations in bipolar disorder have also been linked to irregular transcriptional activity and splicing (Bei *et al.* 2009; Watanuki *et al.* 2008), altered heat shock proteins (Bei *et al.* 2013), and epigenetic modulation of *FKBP5* (Fries *et al.* 2015).

As seen for depression, HPA abnormalities might also influence and predict the development of bipolar disorder and vice versa. In a 3-year follow-up study in young adults, previously high mean daytime cortisol levels significantly predicted the development of both depression and bipolar disorder (Ellenbogen *et al.* 2011). Another study showed that subjects with bipolar disorder with more previous episodes (manic or depressive) had higher mean cortisol levels and a blunted response and flatter diurnal slopes compared with those with fewer previous episodes (Havermans *et al.* 2011). These results have similarly been seen for hair cortisol concentration, which is positively associated with the number of prior mood episodes in patients with bipolar I disorder (van den Berg *et al.* 2020).

Finally, offspring of parents with bipolar disorder were found to have higher salivary cortisol levels compared with offspring of parents with no mental health disorder, independent of confounders such as medication or differences in diagnosis, but sex was not accounted for (Ellenbogen *et al.* 2004, 2010). Findings are not univocal, and there is also evidence of no significant difference in cortisol levels between the offspring of patients with bipolar disorder and offspring of healthy control subjects (Deshauer *et al.* 2006).

HPT Axis

HPT alterations have been reported in subjects with bipolar disorder (Barbuti *et al.* 2017). For example, significantly decreased free and total T_3 and TSH levels and increased free T_4 levels have been reported in unmedicated patients with bipolar II disorder (Lai *et al.* 2021). Interestingly, individuals with bipolar disorder seem to be particularly vulnerable to variations in thyroid function within the normal range, and HPT hypofunction may predict slower treatment response in bipolar depression (Cole *et al.* 2002). Hypothyroidism, with high TSH levels, is a frequent finding in bipolar disorder (Ezzaher *et al.* 2011), and it has been related to more severe features, such as rapid cycling (Bauer *et al.* 1990). Moreover, increased TSH is associated with increased risk of manic relapse (Amann *et al.* 2017), and low T_4 is associated with increased severity of mania and mood instability (more mood episodes, both manic and depressive) (Frye *et al.* 1999). TSH levels in people with bipolar depression are higher than the levels measured in study participants with unipolar depression or with schizophrenia (Wysokinski and Kloszewska 2014). In addition, patients with bipolar disorder have shown higher mean thyroid volumes (Ozsoy *et al.* 2010) and increased T_3 levels (Krishna *et al.* 2013) in comparison with healthy control subjects. These findings suggest that an imbalance in the HPT axis, either hypoactivation or hyperactivation, may be related to all phases of bipolar disorder.

As we will discuss later, treatment with lithium is well known to cause hypothyroidism, altering thyroid functionality and volume. However, lithium-naive patients with bipolar disorder also show abnormalities. Lithium-free bipolar patients show higher mean thyroid volumes and lower T_4 levels compared with control subjects (Ozsoy *et al.* 2010). Furthermore, Kraszewska *et al.* (2019) demonstrated that the percentage of hypothyroidism in lithium-treated and untreated patients was similar, suggesting changes within the HPT axis may possibly be directly related to bipolar disorder.

As seen in unipolar depression, thyroid peroxidase antibodies are frequently elevated in subjects with bipolar disorder (Bocchetta *et al.* 2016). Besides thyroid peroxidase antibodies, thyroglobulin antibodies have been demonstrated to be elevated in individuals with bipolar disorder compared with healthy subjects (Barbuti *et al.* 2017). Most of these findings were observed in those with certain bipolar disorder specifiers: in rapid cycling, with mixed features, or in bipolar depression. In a twin study (Vonk *et al.* 2007), subjects with bipolar disorder had significantly higher levels of thyroid peroxidase antibodies compared with their nonbipolar co-twins. This suggests that thyroid autoimmunity may act as an endophenotype for bipolar disorder, although results are conflicting, and different studies did not confirm these findings (Cobo *et al.* 2015). Moreover, offspring of subjects with bipolar disorder are more susceptible to thyroid autoimmunity. Hillegers *et al.* (2007) noticed a larger percentage of thyroid peroxidase antibody positivity in female bipolar offspring compared with healthy control subjects, and the majority of these thyroid peroxidase antibody-positive individuals also had raised levels of TSH. Susceptibility to autoimmunity seems to be independent of the child's risk of developing a psychiatric disorder, but further research is needed. The exact role of sex in thyroid autoimmunity in people with bipolar disorder is still unclear. Cobo *et al.* (2015) found that TSH and T_4 levels were not affected by sex, even if women had greater thyroglobulin antibody and thyroid peroxidase antibody positivization. Other authors found no significant correlation between sex and thyroid autoantibodies (Kupka *et al.* 2002).

HPG Axis

The HPG axis has been implicated in the development of bipolar and related disorders. Women with bipolar disorder have significantly higher rates of early-onset menstrual cycle dysfunction compared with women with unipolar depression and healthy control subjects (Joffe *et al.* 2006). In fact, menstrual dysfunction may precede the diagnosis of bipolar disorder, as suggested by Rasgon *et al.* (2000). This hypothesis was confirmed in 50% of the women in a larger study from the same group (Rasgon *et al.* 2005). Additionally, the study found that preexisting menstrual cycle abnormalities were associated with increased 17a-OH progesterone, LH/FSH ratio, and free testosterone, suggesting HPG axis dysfunction in these patients. However, most of these studies reported small sample and effect sizes, limiting the translational impact of these findings in a clinical setting. Menstrual cycle dysfunction in bipolar disorder has also been associated with changes in testosterone levels (O'Donovan *et al.* 2002; Rasgon *et al.* 2005).

Interestingly, testosterone levels were found to be positively correlated with the number of manic episodes and the number of suicide attempts in both males and females (Sher *et al.* 2012). This latter finding was further confirmed in a longitudinal study of the same group. In female patients with bipolar disorder, higher baseline testosterone levels predicted suicide attempts in a 2.5-year follow-up period (Sher *et al.* 2014). However, results are conflicting. Indeed, in the previously reported study by Feng *et al.* (2019), the authors found that first-episode patients with bipolar disorder showed reduced testosterone secretion.

Obviously, there is a substantial difference between male and female hormonal physiologies. Wooderson *et al.* (2015) reported that women with bipolar disorder had significantly higher testosterone levels compared with female control subjects, whereas men with bipolar disorder had lower testosterone levels compared with male control subjects. Thus, sex differences need to be considered in further research.

Hypothalamic-Neurohypophyseal System

Only very few studies have analyzed AVP in patients with bipolar disorder, mostly in depressive phases and in mixed samples of individuals with bipolar disorder or MDD, with no conclusive results (Rutigliano *et al.* 2016). Ozsoy *et al.* (2009) found significantly lower oxytocin levels in depressed patients (unipolar and bipolar) compared with healthy control subjects, but only in females. On the other hand, some studies on patients with bipolar disorder reported heightened oxytocin levels (Lien *et al.* 2017; Turan *et al.* 2013). In a recent postmortem study on patients with a major psychiatric disorder, the authors found that a diagnosis of MDD or bipolar disorder was associated with significantly increased oxytocin receptor mRNA levels in the dorsolateral prefrontal cortex (Lee *et al.* 2018). Remarkably, in subjects with either MDD or bipolar disorder, a specific SNP of the oxytocin receptor gene was associated with suicide attempt history (Parris *et al.* 2018).

Schizophrenia Spectrum and Other Psychotic Disorders

HPA Axis

HPA axis abnormalities have been demonstrated in individuals with psychosis and schizophrenia spectrum disorders. Recent meta-analyses have found evidence for elevated blood cortisol levels in individuals with first-episode psychosis (FEP), with larger effect sizes in studies investigating antipsychotic-naive participants (Borges *et al.* 2013; Hubbard and Miller 2019). Girshkin *et al.* (2014) analyzed morning cortisol levels in schizophrenia and found that participants free of antipsychotic medication similarly displayed significantly higher morning cortisol levels compared with control subjects, and higher morning cortisol levels were found in medication-free participants compared with those medicated. In addition, in individuals with FEP, antipsychotic medications can normalize the diurnal cortisol hypersecretion, but not the blunted CAR (Mondelli *et al.* 2010). These analyses provide evidence for HPA axis dysregulation in patients with psychotic disorders and suggest a dampening effect of antipsychotic medication on blood cortisol levels.

Thus, studying high-risk or medication-naive individuals is a valuable approach that may provide insight into HPA axis activity not confounded by medication. Prior studies investigating patients at high risk of developing psychosis found associations between those displaying prodromal and psychotic symptoms and increased cortisol levels (Corcoran *et al.* 2012; Mittal and Walker 2011). More recently, Cullen *et al.* (2020) found a direct connection between elevated cortisol levels and individuals who subsequently converted to psychosis, suggesting that HPA axis dysregulation begins before onset of disease. Additionally, pituitary volume enlargement has been shown to predict onset of psychosis in ultra-high-risk individuals (Garner *et al.* 2005) and has also been observed in FEP (Buschlen *et al.* 2011) and schizophrenia (Takahashi *et al.* 2018). Interestingly, one study found pituitary gland enlargement in unaffected relatives of patients with schizophrenia, suggesting a potential genetic association (Mondelli *et al.* 2008); however, more recent studies have not found such abnormalities (Cullen *et al.* 2015; Habets *et al.* 2012).

Recently, a meta-analysis investigated the concordance between naturally occurring psychosocial stressors and cortisol levels in individuals with established psychosis, high-risk subjects, and healthy control subjects (Cullen *et al.* 2020). There were no significant differences in cortisol response to psychosocial stressors between any of the groups, suggesting cortisol abnormalities in psychosis spectrum disorders are more likely due to the accumulation of global physiological dysregulation rather than to greater sensitivity to psychosocial stressors (Cullen *et al.* 2020). It should be noted that there was heterogeneity between studies and small numbers of participants; thus, further research is required.

As seen in depression and bipolar disorder, GR dysfunction is present in individuals with psychosis. Both first-episode unmedicated and chronic schizophrenia patients have decreased GR mRNA levels compared with control subjects (Liu *et al.* 2020; Sinclair *et al.* 2011), while patients with chronic schizophrenia have lower GR and neuron-specific enolase mRNA expression compared with those with first-episode schizophrenia (Liu *et al.* 2020). This difference suggests additional HPA axis dysregulation as schizophrenia progresses. However, it is difficult to identify the effect of treatments for psychosis in such a relationship. Furthermore, in a group of high-risk females with the same cortisol levels, increased GR expression was associated with increased conversion to psychosis (Iftimovici *et al.* 2020), indicating a role for genetic and epigenetic regulation. Thus, these studies provide a possible contributing cause for the HPA axis dysregulation discussed above.

In individuals with FEP, cortisol levels independently predict a smaller left hippocampal volume (Mondelli *et al.* 2011). In addition, patients with FEP who do not respond to treatments have markedly lower CAR at baseline, which persists after 12 weeks (Mondelli *et al.* 2015).

HPT Axis

Although the exact relationship between the HPT axis and psychotic disorders is unclear, multiple studies have found an association between abnormal thyroid hormone status and schizophrenia. Serum levels of total T_4 have been found to be elevated in acutely ill schizophrenia patients, with a positive correlation between T_4 levels, severity of illness, and degree of clinical response to antipsychotic treatment (Baumgartner *et al.* 2000). In a more recent study of 486 inpatients with schizophrenia, total T_3 and T_4 levels were significantly lower in both first-episode and recurrent schizophrenia patients compared with control subjects (Zhu *et al.* 2020); thus, the exact direction of HPT axis dysregulation is not clear. Nevertheless, free T_3 and T_4 are repeatedly elevated in FEP and acute schizophrenia (Jose *et al.* 2015; Zhu *et al.* 2020). There is also a correlation between free T_3 and T_4 levels and severity of disease, suggesting an association between thyroid hormone levels and severity of symptoms in schizophrenia (Jose *et al.* 2015; Sim *et al.* 2002).

When first-episode and recurrent schizophrenia are compared, first-episode individuals have significantly higher free T_3 and T_4 levels, and significantly lower TSH levels, than patients with recurrent schizophrenia (Zhu *et al.* 2020). Additionally, high rates of hypothyroidism have more frequently been reported in patients with schizophrenia spectrum disorders compared with those without (Hendrie *et al.* 2014; Radhakrishnan *et al.* 2013). These results indicate a change in HPT axis regulation with disease progression, possibly due to the addition of antipsychotic drug treatment.

HPG Axis

Gender and sex hormone differences in schizophrenia are widely reported and affect disease onset, symptoms, and disease progression (Gogos *et al.* 2019). For example, women manifest more positive and affective symptomatology compared with men (Goldstein and Link 1988) and have lower remission and relapse rates (Ochoa *et al.* 2012). Furthermore, throughout a woman's life, psychotic episodes are less common during pregnancy and the luteal phase of the menstrual cycle, when estrogen is increased (Bergemann *et al.* 2007), and more common during times of estrogen withdrawal, such as postpartum and during menopause (Kendell *et al.* 1987; Mahe and Dumaine 2001). There is a midlife increase in female diagnoses of schizophrenia correlating with menopause, with twice as many women as men being diagnosed after age 40 (Riecher-Rossler 2017). Therefore, this literature suggests that fluctuations in estrogen play a role in symptoms and onset of schizophrenia spectrum disorders.

Low serum estradiol and progesterone are reported in both men and women with schizophrenia (Belvederi Murri *et al.* 2016; Bergemann *et al.* 2007; Dogan Bulut *et al.* 2016), with a positive correlation between estradiol level, progesterone level, and score on the Scale for the Assessment of Negative Symptoms (SANS) in men (Dogan Bulut *et al.* 2016). However, in a study of first-episode antipsychotic-naive patients with schizophrenia, higher baseline levels of progesterone were seen in unmedicated than in medicated patients (Cai *et al.* 2018), suggesting that antipsychotic medication may impact HPG regulation. In this study, it was suggested that lower baseline levels of progesterone may be predictive of better therapeutic outcome following antipsychotic treatment.

A recent meta-analysis also found elevated dehydroepiandrosterone-sulphate (DHEA-S) and free testosterone in male and female patients with FEP, and elevated

total testosterone in acutely relapsed schizophrenia patients (Misiak *et al.* 2018). An inverse correlation has repeatedly been seen between testosterone levels and negative scores at the Positive and Negative Syndrome Scale (PANSS) in men, suggesting that testosterone plays a role in the severity of negative symptoms (Ko *et al.* 2007; Sisek-Sprem *et al.* 2014). These findings indicate HPG axis dysfunction in schizophrenia; however, the mechanisms underlying these hormonal changes are unclear and thus further investigation is required.

As discussed, concentrations of both estrogens and androgens during pregnancy may influence the development of mental changes in the postpartum period (Parizek *et al.* 2014). Notably, postpartum psychosis might mirror the acute changes in sex hormones that occur within the first hours and days after delivery, in contrast to postpartum depression, which usually occurs weeks later (Sawyer *et al.* 2019).

Hypothalamic-Neurohypophyseal System

Both oxytocin and AVP levels are altered in psychosis. In their study on male patients with nonacute schizophrenia, Jobst *et al.* (2014) found significantly lower plasma levels of both oxytocin and AVP in patients compared with control subjects. Results are not consistent throughout the literature. Rubin *et al.* (2014) observed significantly lower AVP levels in individuals with schizophrenia and their relatives compared with control subjects, but no differences in oxytocin levels. Postmortem studies revealed low AVP mRNA expression in hypothalamic PVN in individuals with schizophrenia compared with controls (Busch *et al.* 2019). Conversely, another study reported lower plasma oxytocin levels in schizophrenia subjects compared with control subjects, but no differences in AVP levels (Aydin *et al.* 2018). Also, SNPs of the oxytocin receptor have been associated with schizophrenia. Haram *et al.* (2016) found that rs237902 was associated with disorder-specific low amygdala activation, measured at the fMRI189. This same SNP was associated with negative symptoms of schizophrenia in a study by Montag *et al.* (2013), in which two other SNPs (rs53576 and rs237885) were found to be associated with a diagnosis of schizophrenia.

Trauma-and Stressor-Related Disorders

HPA Axis

HPA axis abnormalities are present in PTSD but vary across individuals and groups because of the frequent association with confounding factors (e.g., gender, developmental timing of trauma) and comorbid psychiatric disorders (especially depression). Therefore, PTSD's associations with neuroendocrine conditions are complicated and often not single-faceted (D'Elia *et al.* 2021). Studies of male combat veterans with PTSD demonstrated both enhanced cortisol suppression in response to dexamethasone and low cortisol levels (Wahbeh and Oken 2013; Yehuda 2002). However, participants differ in respect to comorbid diagnoses, with a large proportion having depression or depressive symptoms. Nevertheless, in a meta-analysis that excluded studies investigating PTSD with comorbid disorders, morning salivary cortisol levels were still found to be lower in patients with PTSD compared with controls (Pan *et al.* 2018). Female domestic violence or childhood abuse survivors with PTSD similarly show enhanced cortisol suppression in response to dexamethasone and low morning plasma cortisol levels, regardless of comorbid depression (Griffin *et al.* 2005; Stein *et al.* 1997),

thus providing evidence for enhanced negative feedback inhibition in PTSD, as opposed to what has been observed in depression (Yehuda 2002). Additionally, cerebrospinal fluid CRH concentrations have been found to be higher in patients with PTSD than in healthy controls, whereas ACTH response was blunted, suggesting a downregulation of CRH receptors within the anterior pituitary of these patients (Bremner *et al.* 1997). However, more recent research has found that women who developed PTSD after a sexual assault had higher cortisol levels at 10 P.M., greater CAR, and higher ACTH levels compared with control subjects, and ACTH levels increased with PTSD severity (D'Elia *et al.* 2021). Forty-six percent of these participants had comorbid depression; thus, an interaction between depression pathophysiology and HPA axis regulation may have been present. This comorbidity would explain the elevated ACTH and cortisol levels seen in depressed patients, in contrast to the decreased levels commonly seen in PTSD.

Yehuda *et al.* (2015) demonstrated decreased GR methylation in PTSD patients without comorbid depression compared with those with comorbid depression, providing a possible explanation for the differences in HPA axis response and GR sensitivity. Interestingly, differences in cortisol reactivity after recalling past traumatic events have been seen in PTSD patients with comorbid depression compared with those without. In a study of 60 survivors of the World Trade Center attacks, participants were asked to recall their escape from the attacks (Dekel *et al.* 2017). Following recollection, salivary cortisol levels were measured and were significantly decreased in the group with comorbid depression, were significantly increased in the PTSD-only group, and remained the same in the no-pathology group. These findings suggest that HPA axis pathophysiology in individuals with PTSD and comorbid symptoms differs from that in individuals with PTSD alone.

HPT Axis

Research on the relationship between HPT axis regulation and PTSD is limited; however, there is some evidence for an association between exposure to civilian trauma or combat and abnormal HPT axis activity. In World War II veterans, elevated serum total and free T_3 levels were observed (Wang and Mason 1999), and earlier research of combat veterans also found elevated levels of total T_3, free T_3, and total T_4 (Mason *et al.* 1994). Additionally, significantly lower TSH levels were found in 39 civilians with unmedicated PTSD compared with control participants when background variables were controlled (Olff *et al.* 2006). However, a recent meta-analysis involving 10 observational studies and 373 participants with PTSD reported higher levels of total and free T_3 in PTSD subjects compared with control subjects, whereas no differences were seen in TSH levels and total and free T_4 levels (Toloza *et al.* 2020).

HPG Axis

Epidemiological studies have repeatedly found that women develop PTSD around twice as frequently as men following exposure to trauma; thus, being female is one of the best-known risk factors for PTSD (Gogos *et al.* 2019). It has been hypothesized that these differences are mediated by changes in levels of gonadal hormones such as estrogen, which has a role in fear extinction (Maddox *et al.* 2018). For example, among women with PTSD, those who had low estradiol levels showed stronger intrusive memories following fear conditioning procedures (Wegerer *et al.* 2014) and increased PTSD symptoms in comparison with those who had high estradiol levels (Glover *et al.* 2012). Therefore, these studies suggest a possible role for estrogen in risk and severity of PTSD. However, clinical data are limited and are derived from small numbers of participants. More research into the association and mechanisms of HPG axis regulation in PTSD is needed.

Hypothalamic-Neurohypophyseal System

Evidence on hypothalamic-neurohypophyseal system alterations in trauma-related disorders is still scarce. Recent research suggests that oxytocin and AVP levels do not differ between individuals with PTSD and control subjects (Engel *et al.* 2019, 2021). However, some data suggest that people with PTSD may have lower oxytocin levels compared with healthy subjects (Carmassi *et al.* 2021).

Clinical Implications

The neuroendocrine system has a fundamental role in mental illnesses. Recognizing and acting on specific neuroendocrine components may open new paths for diagnosis, treatment, and prevention of psychiatric disorders. Notably, several psychiatric treatments act on the neuroendocrine system. On the other hand, different medications specifically targeting this system (at different levels) are currently under investigation for psychiatric disorders, and new ones may be developed in the upcoming years. Nevertheless, there are no conclusive results yet, and further research is required. In this section, we provide an overview of the different neuroendocrine systems and their potential implications for clinical psychiatry.

Hypothalamic-Pituitary-Adrenal Axis

The HPA axis has been increasingly studied as a potential target for treatment of different psychiatric disorders. The importance of this axis in psychiatric treatment is further confirmed by the fact that almost every psychotropic drug influences the HPA axis (Subramaniam *et al.* 2019). Antidepressants are mainly--but not always--associated with a reduction in cortisol levels, both basal and postdexamethasone/CRH suppression test, while psychostimulant medications are more frequently associated with an increase (or no changes) in basal cortisol levels (Subramaniam *et al.* 2019).

It is particularly important to highlight the clinical value of GR. Medications for depression require GR in order to exert their antidepressant action (Anacker *et al.* 2011). In fact, antidepressants activate GR in order to increase neurogenesis, while cortisol exerts the opposite effect (Pariante 2017). Binder *et al.* (2004) demonstrated, in a sample of depressed subjects, that specific *FKBP5* SNPs were linked with treatment response. Similar findings were reported by Ising *et al.* (2019). They demonstrated increased expression levels of *FKBP5* and its product, FKBP51, to be associated with nonresponse to antidepressant treatment in depressed individuals. In another recent systematic review (Fischer *et al.* 2019b), the authors demonstrated specific SNPs and haplotypes in genes related to CRH (*CRHBP*, *CRHR1*) and melanocortins (*POMC*) were predictive of nonresponse to antidepressants. They nonetheless reported inconclusive findings on GR- and MR-related genes. In the BIODEP study, the authors found that resistance to antidepressants was associated with lower expression of GR mRNA together with high expression of proinflammatory mRNAs (Cattaneo *et al.* 2020). These findings support the notion that the increased inflammation in depression is associated with glucocorticoid resistance, at least as indicated by the low expression of GR mRNA. Given this evidence, it is not surprising that adjunctive treatment with anti-inflammatory medications is a treatment strategy currently in clinical trials, with the aim of targeting inflammation in individuals with elevated levels of inflammatory biomarkers (Nettis *et al.* 2021). In addition, serotonergic transmission is crucial to both antidepressants and HPA axis functioning. Long-term treatment with antidepressants can indeed modulate serotonergic transmission by acting on serotonin receptors. The serotonergic modulation induced by SSRIs may lead to activation of the HPA axis, which in turn may unfavorably affect serotonin receptor functioning. This mechanism may be--at least partly--responsible for sensitization and/or tolerance to treatment (Fornaro *et al.* 2019).

Different antiglucocorticoid compounds have been studied in mood disorders, mainly as antidepressants (Cleare *et al.* 2015). In their review, Holsboer and Ising (2008) reported the results of two clinical studies on CRH receptor antagonists NBI-30775/R121919 and NBI-34041. Results were encouraging, since the first compound demonstrated a clinical profile that was comparable to the antidepressant paroxetine, and the second one reduced the stress-elicited secretion of cortisol. Mifepristone is a potent competitive GR antagonist and has been evaluated in the treatment of depression, both as augmentation and as monotherapy (Maric and Adzic 2013). Mifepristone has also been trialed in the treatment of bipolar depression, as an adjuvant to current treatment (mood stabilizers, antidepressants, and antipsychotics) (Young *et al.* 2004). A significant improvement in depression rating scores was seen in patients taking mifepristone compared with placebo. Furthermore, significant improvements in neurocognitive functioning were observed. Interestingly, mifepristone has also demonstrated effectiveness in reducing psychotic symptoms in depression with psychotic features (Block *et al.* 2018). On the other hand, Ferrier *et al.* (2015) found no beneficial effects on depressive symptoms for metyrapone--a competitive inhibitor of 11b-hydroxylase (with resulting inhibition of cortisol)--in patients with treatment-refractory depression. A recent meta-analysis by our research group in individuals with mood disorders (both depression and bipolar disorder) (Lombardo *et al.* 2019) showed that only subjects with higher baseline cortisol levels may benefit from treatment with cortisol synthesis inhibitors, supporting a potential role for cortisol as a predictive biomarker in people with mood disorders.

The neurosteroid allopregnanolone is an FDA-approved treatment for postpartum depression (Walton and Maguire 2019). Among its properties, it acts as a positive allosteric modulator at $GABA_A$ receptors, which may account for its anxiolytic and antidepressant effects. Also, allopregnanolone is involved in the stress response system and may regulate HPA axis activity by acting on hypothalamic neurons under protracted stressful conditions (Almeida *et al.* 2021). Therefore, it may be a promising target also for the treatment of trauma-and stressor-related disorders (such as PTSD), but further research is needed.

A recent systematic review highlighted the potential procognitive effects of the glucocorticoid precursor pregnenolone in individuals with schizophrenia (Soria *et al.* 2018). Another systematic review in the Cochrane Schizophrenia Group's Trials Register analyzed data from 11 studies that randomly assigned treatment conditions to

509 people with schizophrenia, schizoaffective disorder, or psychotic depression, comparing antiglucocorticoids and related drugs with placebo (Garner *et al.* 2016). Even though further research is needed, preliminary evidence suggests a beneficial effect for mifepristone (with few overall adverse effects) compared with placebo (Garner *et al.* 2016).

Another recent systematic review and meta-analysis involving 362 participants from eight randomized controlled trials (RCTs) demonstrated that administration of hydrocortisone could be effective in the prevention of PTSD symptoms, but not in their treatment (Kothgassner *et al.* 2021).

Finally, an important role is played by the gut microbiota, which is profoundly linked to the HPA axis. The gut microbiota includes all the indigenous microorganisms that live in the human gut. This assemblage of microorganisms has an important role in mediating the response to stress (Baumgartner *et al.* 2000; Farzi *et al.* 2018; Sudo 2014). Perturbations in gut microbiota composition have been transdiagnostically associated with different psychiatric conditions, including depression, bipolar disorders, and schizophrenia (Nikolova *et al.* 2021). Moreover, the gut microbiota seems to be involved in treatment resistance in both depression (Fontana *et al.* 2020) and schizophrenia (Manchia *et al.* 2021). Notably, probiotics are now emerging as a new potential adjunctive treatment for different psychiatric diseases, such as depression (Butler *et al.* 2019; Vlainic Vlainic *et al.* 2016).

Hypothalamic-Pituitary-Thyroid Axis

Different psychotropic medications may affect the HPT axis as well. Lithium is one of the most effective treatments for bipolar disorder, and hypothyroidism--with a reduction of circulating levels of thyroid hormones--is one of the most common side effects of long-term lithium use. Nevertheless, several studies reported that the increased presence of thyroid peroxidase antibodies in patients with bipolar disorder compared with control subjects was not associated with lithium exposure (Barbuti *et al.* 2017; Kupka *et al.* 2002). Also, other psychotropic medications may affect thyroid function. In their recent study on patients with bipolar disorder, Li *et al.* (2019) found no differences in thyroid profiles in patients with different mood episodes; they did find, however, that treatment with quetiapine could affect thyroid function, significantly reducing levels of thyroid hormones. Following antipsychotic drug treatment, free T_3 and T_4, total T_4, and reverse T_3 levels decrease or normalize, while TSH levels increase, thus suggesting an interaction between thyroid hormone metabolism and antipsychotic medication (Baumgartner *et al.* 2000; Bunevicius *et al.* 2014; Santos *et al.* 2012). The decrease in total T_4 following an antipsychotic medication regimen is correlated with clinical response, indicating that normalization or reduction of HPT axis hormones can be a parameter for measuring recovery (Baumgartner *et al.* 2000; Santos *et al.* 2012).

Most of the evidence on the HPT axis and treatment of psychiatric diseases comes from studies of mood disorders, especially depression. Even though it is obvious that thyroid hormone supplementation is beneficial in hypothyroidism, there is evidence that it may also improve depressive symptoms in patients with a normal thyroid function. Notably, augmentation with T_3 has demonstrated efficacy in treatment-resistant depression (Carvalho *et al.* 2009). In addition, T_4 may have neuroprotective effects by acting on BDNF, with a mechanism similar to antidepressants (Hung *et al.* 2013). Interestingly, Baek *et al.* (2014) found an association between higher TSH levels and lower baseline and reduced increase in BDNF levels during antidepressant treatment. Thus, they suggest the HPT axis may be crucial in mediating the antidepressant response.

Even though only very few studies have examined the use of T_3 in bipolar depression, findings are encouraging (Parmentier and Sienaert 2018). Clinical trials involving patients with rapid-cycling bipolar disorder demonstrated that treatment with levothyroxine was associated with significantly less time in a depressed or mixed state, and more time in a euthymic state, compared with placebo (Walshaw *et al.* 2018). In addition, both subclinical hypothyroidism and higher TSH levels still within the normal range (> 2.5 mIU/mL) have been associated with poorer antidepressant response in unipolar and bipolar depression (Cohen *et al.* 2018). Thus, the optimization of TSH levels with thyroid hormone supplementation may be an effective treatment strategy in depressed patients with high-normal TSH levels and poor antidepressant response (Cohen *et al.* 2018).

Hypothalamic-Pituitary-Gonadal Axis

Several psychotropic medications may affect the HPG axis--mainly antipsychotics and antidepressants, but also mood stabilizers (Drobnis and Nangia 2017). In fact, both first-and second-generation antipsychotics can antagonize dopamine receptors (mainly D_2), increasing the levels of prolactin and decreasing the release of gonadotropin. Hyperprolactinemia may be a clinical issue both in women and in men. It usually manifests with infertility and sexual dysfunctions. Chronically, it may lead to osteolysis. There are, however, important differences between different molecules. For example, with certain second-generation compounds, such as aripiprazole and cariprazine, which are partial agonists of dopamine receptors, these effects are markedly reduced. Also, several antidepressants with serotonergic activity, including SSRIs, monoamine oxidase inhibitors (MAOIs), and some tricyclics, may increase prolactin levels by acting on dopamine signaling (inhibition of the reuptake) (Torre and Falorni 2007). Lithium also has been demonstrated to increase prolactin and LH and to decrease sex hormones levels. Lastly, anticonvulsants may decrease free or bioavailable testosterone, with variable effects on the other reproductive hormones (Drobnis and Nangia 2017). In particular, valproate has been associated with high rates of menstrual abnormalities, hyperandrogenism, and polycystic ovary syndrome (O'Donovan *et al.* 2002).

Even though sex is always a variable to account for, there is some evidence pointing to the role of both testosterone and estrogens in mental well-being, independent of sex. McHenry *et al.* (2014) discussed in their review the antidepressant effects of testosterone in both women and men. A proposed mechanism to explain this potential effect is the activation of the hippocampal mitogen-activated protein kinase (MAPK) pathway. Therefore, supplementation with testosterone (intramuscular, transdermal, or oral) has been evaluated as an adjunctive treatment for depressed men, especially for partial responders with low or borderline testosterone levels (Kanayama *et al.* 2007). Pope *et al.* (2003) reported that testosterone transdermal gel was effective in reducing depressive symptoms in male subjects with refractory depression and low or borderline testosterone levels. However, these findings were not replicated in a subsequent larger study of the same group, in which testosterone supplementation failed to significantly reduce depressive symptoms compared with placebo (Pope *et al.* 2010). Despite conflicting findings, a recent meta-analysis of 27 placebo-controlled RCTs confirmed the efficacy and effectiveness of testosterone in reducing depressive symptoms in men, particularly at a high dosage (Walther *et al.* 2019). Treatment with testosterone is relatively safe, especially if testosterone levels are kept in the normal range. However, long-term effects on major cardiovascular events and prostate cancer risk are still uncertain (dos Santos and Bhasin 2021). Also, low-dose transdermal testosterone was found to improve depressive symptoms in women with treatment-resistant depression (Miller *et al.* 2009). This antidepressant effect with low doses of testosterone may be due to a greater sensitivity to androgens in women compared with men. In their study of treatment-resistant depression in women, Huang *et al.* (2008) reported that menopausal status and ovarian steroid levels (but not age) were the main determinants of antidepressant efficacy of repetitive transcranial magnetic stimulation, both in MDD and in bipolar disorder. Notably, perimenopausal depression may be directly associated with the fall in ovarian estrogen production (estradiol withdrawal). Therefore, hormone replacement therapy (with estradiol) may be a promising strategy to treat or prevent the development of depression in susceptible women (Schmidt and Rubinow 2009; Schmidt *et al.* 2015).

There is ongoing research on the use of adjunctive hormone therapies for treatment of schizophrenia. Administering 17b-estradiol or ethinyl estradiol alongside stable antipsychotic use has been shown to significantly decrease PANSS positive, general, and total symptoms in female schizophrenia or schizoaffective disorder patients compared with placebo groups (Akhondzadeh *et al.* 2003; Kulkarni *et al.* 2015). Furthermore, in a cross-sectional study of postmenopausal women with schizophrenia, users of hormone replacement therapy received lower average daily doses of antipsychotic medication and had less severe negative symptoms compared with non-users of hormone replacement therapy (Lindamer *et al.* 2001). However, despite these positive results, estradiol (especially at an efficacious dose) may have serious health risks, such as thromboembolism and endometrial hyperplasia (Gogos *et al.* 2015). Therefore, further research is required on the underlying mechanisms of protective effects of estrogens, along with the potential for estrogen treatment in men. In women with schizophrenia, menstrual cycle irregularity was associated with poorer cognitive performance (Gurvich *et al.* 2018). Notably, the selective estrogen receptor modulator raloxifene has demonstrated beneficial effects on cognition in schizophrenia (Soria *et al.* 2018).

We already discussed how the interconnection between the HPG and the HPA axes may be critical in the relationship between HPG and psychiatric disorders. In this regard, Mou *et al.* (2017) demonstrated antidepressant properties of the ginsenoside Rg1 in mice. Rg1 is an active compound of the plant genus *Panax* (ginseng) that exerts several biological functions, including sex hormone-like activities and GR modulation. Notably, mice treated with Rg1 presented significantly lessened depressive-like symptoms, together with reduced glucocorticoid levels and increased testosterone levels, in comparison with untreated mice.

Hypothalamic-Neurohypophyseal System

Given the evidence we discussed on the neurohypophyseal system and its connections with other neuroendocrine and immune pathways, it is not surprising that AVP and oxytocin have been studied for their therapeutic potential in psychiatric disorders.

Antagonism of the AVP receptor AVPR1b has been demonstrated to have antidepressant effects (Neumann and Landgraf 2012). Nevertheless, Griebel *et al.* (2012) found no conclusive evidence from three randomized double-blind, placebo-controlled studies involving depressed individuals taking an AVPR1b antagonist (SSR149415) for 8 weeks. Notably, several psychotropic medication classes, such as antidepressants (mainly SSRIs, but also tricyclics, MAOIs, and venlafaxine) and anticonvulsants (such as valproic acid, carbamazepine, and oxcarbazepine), may affect AVP levels and cause SIADH (Liamis *et al.* 2008; Spasovski *et al.* 2014). The precise mechanisms of this biological effect have yet to be clarified. However, the increase in AVP secretion may be caused by the effects on serotonin and norepinephrine transmission (De Picker *et al.* 2014) or by a direct effect on renal sensitivity to AVP (Sachdeo *et al.* 2002).

There is preclinical and clinical evidence that oxytocin, both peripherally and centrally administered, may counteract depression (Matsuzaki *et al.* 2012; Neumann and Landgraf 2012). In addition, these antidepressant effects remain even after the administration of an oxytocin receptor antagonist (Acevedo-Rodriguez *et al.* 2015). This evidence suggests that the antidepressant effects are differently mediated, perhaps as a result of the crosstalk with AVP receptors (Manning *et al.* 2012). Also, oxytocin can increase dopamine transmission, through D_1 receptor activation, in the medial prefrontal cortex, thus exerting antidepressant effects (Li *et al.* 2020). There is still active debate on the effectiveness of oxytocin administration to prevent postpartum depression. Some evidence suggests that oxytocin may negatively affect maternal mood (Kroll-Desrosiers *et al.* 2017; Mah 2016). However, other findings demonstrate that it can protect against future development of postpartum depression, even without immediate effects on maternal mood (Takacs *et al.* 2019).

Different studies analyzed the efficacy of oxytocin administration in ameliorating psychotic symptoms. Feifel *et al.* (2010) administered intranasal oxytocin (titrated to 40 IU twice a day) to 15 subjects with residual symptoms of schizophrenia for 3 weeks. Oxytocin significantly reduced scores on the PANSS and the Clinical Global Impression (CGI) Scale compared with placebo (Feifel *et al.* 2010). Another trial with a lower dosage (24 IU twice a day) and duration (2 weeks) confirmed a significant effect of intranasal oxytocin on PANSS scores (Pedersen *et al.* 2011). A recent meta-analysis of nine RCTs found that higher doses of intranasal oxytocin may be effective in improving negative symptoms of schizophrenia, with a moderate effect size (Sabe *et al.* 2021). However, this effect disappeared after the exclusion of one outlier, and thus no firm conclusions about this association could be drawn (Sabe *et al.* 2021).

Moreover, oxytocin administration may help to ameliorate the neurocircuitry connectivity dysfunction observed in individuals with PTSD (Crum *et al.* 2021). These findings were only partially confirmed in a recent study demonstrating that intranasal oxytocin (24 IU) modulates threat-related functional connectivity in individuals who were exposed to trauma in childhood (Sippel *et al.* 2021). However, this effect was not mediated by a diagnosis of PTSD and varied as a function of gender and hemisphere.

Conclusion

Mental health is a fundamental element of the whole individual's well-being, and psychiatric disorders are deeply interconnected with biological modifications in our bodies. With its unique focus on mind and body interactions, psychoneuroendocrinology may offer diverse perspectives for approaching mental health. Even though current evidence is still largely exploratory, research in this field may help to identify the biological mechanisms that are causes and/or consequences of psychiatric illnesses. Identifying these mechanisms may ultimately lead to a better characterization of psychiatric diagnoses and treatments.

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CHAPTER 5

Brain-Immune System Interactions

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Multidirectional interactions among psychological factors and the nervous, endocrine, and immune systems form the basis of important physiological pathways that are crucial for maintaining mental and physical health. These multisystem interactions can also mediate the pathological aspects of numerous diseases. Therefore, elucidating brain-immune system pathways and mechanisms is likely to be critically useful for restoring health in the presence of disease or promoting health in the absence of disease. In this chapter we begin with an overview of the immune system and introduce its three major functional dimensions. We then go on to describe the effects of stress and depression on immune function, the association between other psychiatric disorders and the immune system, and the pathways that mediate these effects and associations. The penultimate section covers the pathways that mediate the effects of the immune system on the nervous system and on mental and psychological states. Finally, we discuss the relevance of brain-immune interactions in the context of mental illness and its treatment.

The Immune Triad: Immunoprotection, Immunopathology, and Immunoregulation

The immune system is a highly distributed physiological system. It consists of primary (bone marrow and thymus), secondary (lymph nodes, spleen, tonsils, and parts of mucosal tissues), and tertiary (most other organs in the body) organs; immune cells or leukocytes (granulocytes, monocytes, T cells, B cells, natural killer cells); and humoral factors (e.g., antibodies, cytokines, complement peptides) that traverse the body through a network of vascular and lymphatic vessels. When we are discussing immune responses, it is useful to categorize them in terms of their principal cellular and molecular components. For example, innate, adaptive, and helper T cell (e.g., Th1, Th2, Th17) immune responses are all defined in terms of their cellular, cytokine, and humoral components. In addition to these categories, it is also useful to define immune responses in terms of their integrated functional effects. Dhabhar (2009a, 2009b, 2014, 2018) proposed that immune responses be categorized as being immunoprotective, immunopathological, and immunoregulatory/inhibitory. It is important to bear in mind that although such categories provide useful constructs with which to organize ideas, concepts, and models, an overall in vivo immune response is likely to consist of several types of responses with varying amounts of dominance from each category. The composition and nature of an immune response is also affected by--and changes with--time. The three major types of immune responses are defined below in terms of their functional end effects (Dhabhar 2009a, 2009b, 2014, 2018).

Immunoprotective responses are defined as those that promote efficient wound healing, eliminate infections and cancer, and mediate vaccine-induced immunological memory (Dhabhar 2009a, 2009b, 2018). Key characteristics of immunoprotection include active immune surveillance, a rapid and robust response on immune activation, and efficient clearance of the activating agent or pathogen, followed by rapid resolution. Immunoprotective responses are critical for completion of the proliferative and remodeling phases of wound healing. Wound healing is important not only for frank wounds (where the initiating event is tissue damage itself) but also for tissue-intrinsic "wounds" (where the initiating event is an immune response precipitated by intracellular infection, during which there can be collateral tissue damage). Different types and combinations of immune responses--innate, adaptive, Th1, Th2--can confer immunoprotection, depending on the type of pathogen involved (viral, bacterial, protozoan, fungal, helminthic), on whether the pathogen is intracellular or extracellular, and on the accompanying wounding conditions (sterile, infected, external, or internal wounds).

Immunopathological responses are defined as those that are directed against the self (as in autoimmune diseases such as multiple sclerosis, arthritis, or systemic lupus erythematosus) or against innocuous antigens (asthma, allergies) and responses that are directed against chronic, nonresolving inflammation (Dhabhar 2009a, 2009b, 2018). Immunopathology is also involved in low-level, long-term elevations in local and/or systemic inflammatory mediators (e.g., C-reactive protein [CRP] or interleukin 6 [IL-6]), which are thought to contribute to disorders such as cardiovascular disease, obesity, and depression (Dantzer *et al.* 2008; Maes 1993; Van Gaal *et al.* 2006).

Immunoregulatory responses are defined as those that involve immune cells and factors that regulate (mainly downregulate) the function of other immune cells (Dhabhar 2009a, 2009b, 2018). Although the earlier concept of suppressor T cells became mired in controversy, newer studies suggest that there is an arm of the immune system that functions to inhibit immune responses (Piccirillo 2008; Simpson 2008; Wing and Sakaguchi 2010). For example, $CD4^{+}CD25^{+}Foxp3^{+}$ regulatory T cells, IL-10, and transforming growth factor b have been shown to have immunoregulatory/inhibitory functions. The physiological function of these factors is to keep proinflammatory, allergic, and autoimmune responses in check (Bluestone and Tang 2005; Wing and Sakaguchi 2010). However, it

has also been suggested that immunoregulatory/inhibitory factors may suppress anti-tumor immunity and that their presence may be indicative of a negative prognosis for cancer (Finn 2008; Olson and McNeel 2013; Saul *et al.* 2005; Whiteside 2014).

Effects of the Brain and Behavior on the Body

More than four decades ago, Ader and Cohen (1975) showed that an immune response could be modified through classical Pavlovian conditioning. Numerous studies have confirmed and extended this initial insight and have established beyond argument the ability of brain states to significantly modulate immune system functioning (Bower and Irwin 2016; Irwin and Rothermundt 2012; Kelley and McCusker 2014; Nemeroff 2013; Padro and Sanders 2014; Quan 2014; Schedlowski *et al.* 2014; Straub 2014). The majority of these studies have focused on the effects of stress on the immune response (Dhabhar 2014, 2018; Straub *et al.* 2013).

Effects of Stress on Immune Function

Even though the word *stress* generally has negative connotations, stress is a familiar and ubiquitous aspect of life, representing a stimulant for some individuals but a burden for many others. Numerous definitions have been proposed for the concept of stress, each focusing on aspects of an internal or external challenge, disturbance, or stimulus; on stimulus perception; or on a physiological response (Goldstein and McEwen 2002; McEwen 2002; Sapolsky 2005). An integrated definition states that stress is a constellation of events consisting of a stimulus *(stressor)* that precipitates a reaction in the brain *(stress perception and evaluation)* that activates physiological fight-or-flight systems in the body *(biological stress response)* (Dhabhar and McEwen 1997).

Short-term stress involves changes in stress-related factors that last for minutes to hours, whereas chronic stress involves changes that last for months or years. The only way that a stressor can affect the brain or body is through the biological stress response. Although many factors are involved, the major mediators of stress effects are norepinephrine and epinephrine, which are released by the sympathetic nervous system, and corticotropin-releasing hormone (CRH), adrenocorticotropin, and cortisol, which arise following activation of the hypothalamic-pituitary-adrenal (HPA) axis. Virtually every cell in the body expresses receptors for one or more of these factors. Therefore, stress hormones can induce changes in almost all cells and tissues and inform them about the presence of a stressor. Virtually every type of stressor, ranging from laboratory stressors (e.g., public speaking, mental arithmetic) to life-related stressors (e.g., exercise, process of undergoing surgery, skydiving, bereavement, loneliness, academic examinations), has demonstrated a measurable effect on the immune system (Dhabhar 2014, 2018; Raison *et al.* 2002).

Although stress has a bad reputation, it is important to recognize that the adaptive purpose of a physiological stress response is to promote survival during fight or flight. Whereas long-term stress is generally harmful, short-term stress can be protective in that it prepares the organism to deal with threats or challenges. It has been proposed that a psychophysiological stress response is one of nature's fundamental survival mechanisms that could be therapeutically harnessed to augment immune function during vaccination, wound healing, or infection (Dhabhar 2009a, 2009b, 2014, 2018; Dhabhar and McEwen 1999; Dhabhar and Viswanathan 2005). Mechanisms of acute stress-induced immunoenhancement include the following:

1. Subpopulation-specific changes in neutrophil, macrophage, and lymphocyte redistribution (Dhabhar and McEwen 1997; Dhabhar *et al.* 2012; Rosenberger *et al.* 2009)
2. Increased leukocyte infiltration into sites of immune activation (Viswanathan and Dhabhar 2005)
3. Increased dendritic cell and macrophage maturation and traffic to draining lymph nodes (Viswanathan and Dhabhar 2005)
4. Enhanced local cytokine production, with a key role for interferon-g (IFN-g) (Dhabhar *et al.* 2000)
5. Enhanced systemic production of cytokines such as IL-1 and IL-6, which is also likely to contribute to enhancement of immune function

induced by short-term stress (Aschbacher *et al.* 2012; Puterman *et al.* 2014; Steptoe *et al.* 2001)

The adjuvant-like immunoenhancing effects of short-term stress may have evolved because many stressful situations (e.g., aggression, accident) result in immune activation (e.g., wounding, infection) and vice versa (Dhabhar 2014; Puterman *et al.* 2014). Interestingly, in modern times, many medical procedures involving immune activation (e.g., vaccination, surgery) also induce a stress response. Preclinical findings in animals initially lent support to this hypothesis (Dhabhar and McEwen 1996; Dhabhar *et al.* 1995; Viswanathan and Dhabhar 2005) and subsequently were replicated in humans. Clinical studies have demonstrated that patients undergoing knee surgery who show a robust and adaptive immune cell redistribution profile during the short-term stress of surgery also show significantly enhanced recovery (Rosenberger *et al.* 2009). Similarly, preclinical studies initially demonstrated that short-term stress that was experienced during primary (Blecha *et al.* 1982; Coe *et al.* 1989; Dhabhar and Viswanathan 2005; Viswanathan *et al.* 2005; Wood *et al.* 1993) or secondary (Blecha *et al.* 1982; Dhabhar and McEwen 1996, 1999; Dhabhar *et al.* 2000; Saint-Mezard *et al.* 2003) antigen exposure significantly enhanced the ensuing immune response (Dhabhar 2002). An elegant series of clinical studies has demonstrated that the adjuvant effects of short-term psychological stress, or exercise stress, can enhance vaccine-induced immunity in human subjects (Edwards *et al.* 2006, 2007, 2008).

We have defined chronic stress as that which results in stress-related biological changes that last for weeks, months, or years (Dhabhar and McEwen 1997). Figure 5-1 illustrates the steps and factors that mediate the transition from adaptive short-term stress to deleterious chronic stress.

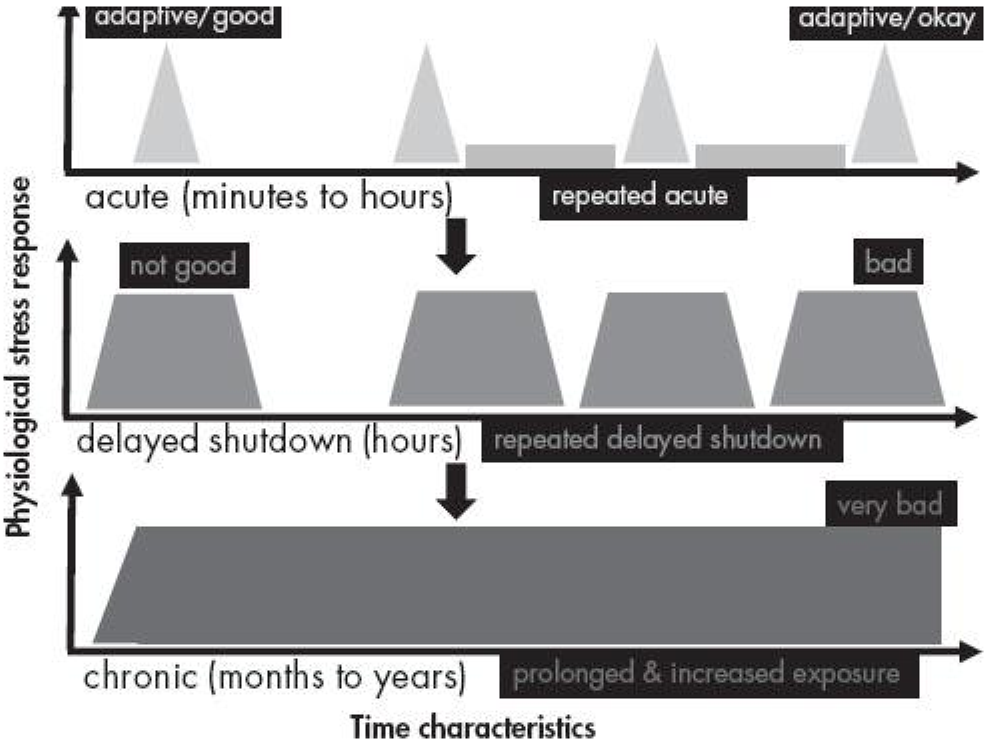

adaptive/good
adaptive/okay
acute (minutes to hours)
repeated acute
not good
bad
delayed shutdown (hours)
repeated delayed shutdown
very bad
chronic (months to years)
prolonged & increased exposure
Physiological stress response
Time characteristics

FIGURE 5-1. Steps and factors that mediate the transition from adaptive short-term stress to deleterious chronic stress.

Time is represented on the x-axis, and changes in stress-related biological factors are represented on the y-axis. The *upright triangle* (**top panel**) represents an adaptive short-term stress response, where stress-related biological changes occur rapidly (within minutes) and resolve back to baseline rapidly (within minutes to hours). Life involves a series of stress "hits" and responses. Most humans and other organisms are built to handle this series of stress responses and can continue to mount adaptive/protective responses under such conditions, especially if their psychological and physiological systems return to baseline/resting conditions (*bars between triangles*) between stress hits. The *trapezoid* (**middle panel**) represents a prolonged short-term stress response with delayed shutdown that results in greater overall AUC (area under the curve) exposure to stress-related factors compared with the prototypical adaptive stress response. Such prolonged stress responses can begin to have deleterious effects, especially if they are part of a series of stress hits with little or no time of return to baseline/resting conditions between hits. The *long trapezoid* (**bottom panel**) is a graphical representation of chronic stress, which is known to have numerous deleterious effects on brain, body, and health and on mental and physical performance.

Source. Reprinted from Figure 2 in Dhabhar FS: "The Short-Term Stress Response--Mother Nature's Mechanism for Enhancing Protection and Performance Under Conditions of Threat, Challenge, and

Opportunity." *Frontiers in Neuroendocrinology* 49:175-192, 2018. Copyright (c) 2018, Elsevier Inc. Used with permission.

In contrast to short-term stress, chronic or long-term stress can be harmful (Dhabhar and McEwen 1997). Chronic stress suppresses or dysregulates innate and adaptive immune responses by altering the type 1-type 2 cytokine balance, inducing low-grade chronic inflammation and suppressing the numbers, trafficking, and function of immunoprotective cells (Dhabhar 2009a, 2009b, 2014). Chronic stress has been shown to increase susceptibility to infections, reduce antibody responses to vaccination, and delay wound healing (Cohen *et al.* 1991; Fagundes *et al.* 2013; Glaser and Kiecolt-Glaser 2005; Irwin 2008; Kiecolt-Glaser *et al.* 1995; Padro and Sanders 2014; Sanders and Straub 2002; Solomon 1969; Straub *et al.* 2013; Vitlic *et al.* 2014; Webster Marketon and Glaser 2008). Chronic stress also has been linked to increased morbidity and mortality in neoplastic diseases (including breast cancer and malignant melanoma), diabetes, and cardiovascular disease (Antoni *et al.* 2006; Ben-Eliyahu 2020; Ben-Eliyahu *et al.* 2007; Dhabhar 2014; Eckerling *et al.* 2021; Evans *et al.* 2005; Fenton and Stover 2006; Leserman *et al.* 1999; Lutgendorf and Sood 2011; Raison and Miller 2003; Saul *et al.* 2005). In addition to significant personal and health-related costs of chronic stress, the annual economic cost to industry arising from work-related stress in the United States is estimated at more than $300 billion (American Psychological Association 2007). Dysregulation of the circadian cortisol rhythm is an important marker that coincides with the deleterious effects of chronic stress (Dhabhar 2014; Dhabhar and McEwen 1997; Saul *et al.* 2005; Sephton and Spiegel 2003).

Key factors that determine whether stress enhances or suppresses immune function include the following (for reviews, see Dhabhar 2009a, 2009b, 2014, 2018):

1. The effects of stress on immune cell distribution in the body
2. The duration (short [minutes to hours] vs. long [weeks to months to years]) of changes in stress-related factors
3. The differential effects of physiological versus pharmacological concentrations of stress hormones and the differential effects of endogenous (e.g., cortisol, corticosterone) versus synthetic (e.g., dexamethasone) hormones
4. The timing of stressor or stress hormone exposure relative to the time of activation and ensuing time course of the immune response

It is important to recognize that factors such as gender, genetics, age, route of administration, nature of the immunizing antigen, and time during the circadian cycle additionally affect immune function and could also affect the nature of the relationship between stress and immune function. It is also important to bear in mind that it is not the effect of a particular stressor in enhancing or suppressing immune function but rather the end effect on the immune response that determines whether stress-immune system interactions have beneficial or harmful effects on health.

Effects of Depression on Immune Function

Numerous studies have investigated the effects of stress-related disorders, especially major depressive disorder (MDD), on immune function (Antonioli *et al.* 2012; Blume *et al.* 2011; Irwin and Miller 2007; Miller and Raison 2016). Despite a significant degree of heterogeneity across individual studies, evidence suggests that patients with MDD demonstrate a number of immune changes similar to those seen in individuals undergoing chronic and/or severe stress (Herbert and Cohen 1993; Zorrilla *et al.* 2001). This finding is hardly surprising, given the many indices of stress system hyperactivity that are apparent in patients with MDD, including increased CRH and cortisol production (Pariante *et al.* 1995) and augmented sympathetic nervous system activity as manifested in part by increased peripheral blood catecholamines (Veith *et al.* 1994; Wong *et al.* 2000). Enumerative immune changes shared by MDD and chronic or severe stress include decreases in lymphocytes, B cells, and T cells and increases in the ratio of CD4 to CD8 T cell subsets (Herbert and Cohen 1993). Shared functional changes include decreases in natural killer (NK) cell activity and lymphocyte proliferation in response to nonspecific mitogens (Table 5-1) (Herbert and Cohen 1993; Zorrilla *et al.* 2001). It is important to note, however, that MDD is a heterogeneous condition, and immune changes are not uniform across all patients. Indeed, inhibited lymphocyte responses tend to be most striking in patients who are older, are hospitalized, or have more severe and/or melancholic types of depression (Miller 1998; Schleifer *et al.* 1989). In addition, the sleep changes common in depression are known to alter lymphocyte responses, especially NK cell activity, even in the absence of other depressive symptoms (Irwin 2015; Irwin *et al.* 1996). Nonetheless, it does not appear that these factors completely account for the association between MDD and alterations in measures of the number and function of lymphocyte subsets (Herbert and Cohen 1993; Irwin and Miller 2007).

TABLE 5-1. Immune alterations in major depressive disorder

Increased white blood cells
Increased neutrophil percentage
Decreased lymphocyte percentage
Increased CD4-to-CD8 ratio
Decreased natural killer cell activity
Decreased mitogen-induced lymphocyte proliferation
Increased circulating interleukin 6
Decreased circulating interleukin 10
Increased haptoglobin
Increased prostaglandin E_2

Evidence suggests that depression, like chronic stress, may impair T cell function in ways that are relevant to disease vulnerability. For example, one study reported that patients with MDD have a marked decrease in the ability to generate lymphocytes that respond to the herpes zoster virus (Irwin *et al.* 1998). Also consistent with impaired T cell function in depression is the observation that depressed patients, especially those with melancholia, demonstrate impaired cell-mediated immunity (CMI), as measured by the delayed-type hypersensitivity response (Hickie *et al.* 1993, 1995). A recent study suggested that a potential interaction between MDD and sex might contribute to susceptibility to cytomegalovirus (CMV); women with MDD were more likely, and men with MDD were less likely, to be CMV positive (Ford *et al.* 2020). Relative to these findings, increasing interest has been generated by evidence that the deleterious effects of chronic CMV infection on white matter integrity may contribute to MDD (Zheng *et al.* 2021).

A growing database also indicates that depression in both medically healthy and medically ill patients is associated with increased immunopathological inflammatory responses (Andrei *et al.* 2007; Kim *et al.* 2007; Lesperance *et al.* 2004; Maes 1999; Miller and Raison 2016; Musselman *et al.* 2001). Findings consistent with inflammatory activation in depression include increased plasma and cerebrospinal fluid (CSF) concentrations of inflammatory cytokines, increased in vitro production of inflammatory cytokines from stimulated peripheral blood mononuclear cells, increased positive acute-phase proteins (and decreased negative acute-phase proteins), increased chemokines and adhesion molecules, and increased production of prostaglandins and reactive oxygen and nitrogen species (Kim *et al.* 2007; Maes 1999; Miller and Raison 2016; Raison *et al.* 2006).

On the basis of meta-analyses, increases in peripheral blood IL-6, tumor necrosis factor (TNF), and CRP are some of the most reliable inflammatory biomarkers associated with depression (Dowlati *et al.* 2010; Howren *et al.* 2009). Of interest, given the role of IL-6 and CRP in predicting disease outcome in both cardiovascular disorders and diabetes (Ridker *et al.* 2000a, 2000b), as well as data indicating that inflammation may play a role in cancer (Aggarwal *et al.* 2006), the relationship between depression and activation of the inflammatory response may provide a mechanism that explains the negative impact of depression on a number of illnesses (Evans *et al.* 2005). Moreover, immune activation in MDD may be involved in several of the pathophysiological changes that are common in the context of depression, including bone loss, increased body temperature, hippocampal volume loss, insulin resistance, hyperlipidemia, and the metabolic syndrome (Miller and Raison 2016; Miller *et al.* 2009).

It is important to recognize that in the absence of chronic infection, cancer, or immunodeficiency disease, modest elevations in antiinflammatory cytokines may exert salubrious or health-protective effects by mediating the resolution of inflammatory processes and preventing or antagonizing the damaging effects of prolonged inflammation. Therefore, it is also important to investigate the role played by antiinflammatory/immunomodulatory cytokines such as IL-10 in depression (Dhabhar *et al.* 2009). In healthy individuals, there is a regulated balance between pro-and antiinflammatory cytokines; for example, IL-6 mediates the early phase of the inflammatory process and induces the release of IL-10, which exerts immunoregulatory effects and resolves inflammation (Daftarian *et al.* 1996; Fang *et al.* 2008; Ogawa *et al.* 2008). The net result of such regulatory relationships is that the immune system can quickly respond to a challenge and subsequently return to homeostasis once the challenge has ended. Short-term inflammatory reactions in response to immune challenges such as wounding or infection are adaptive and essential for survival, but chronic inflammation is harmful. Interestingly, depression is associated with numerous disorders that are thought to involve chronic inflammation (Dantzer *et al.* 2008; Evans *et al.* 2005; Kiecolt-Glaser and Glaser 2002). These include cardiovascular disease (Frasure-Smith *et al.* 2007; McCaffery *et al.* 2006; Musselman and Nemeroff 2000; Whooley *et al.* 2007), obesity (Onyike *et al.* 2003), rheumatoid arthritis (Bruce 2008; Zautra *et al.* 2004), multiple sclerosis (Triantafyllou *et al.* 2008), and cancer (Currier and Nemeroff 2014).

A number of potential factors may contribute to increased inflammatory responses in depressed patients. One factor that has received special attention is BMI. BMI has been reliably correlated with peripheral markers of inflammation, including IL-6, in part related to the capacity of adipocytes to produce inflammatory cytokines (Schaffler *et al.* 2007). Early-life stress is another factor that may be involved. A meta-analysis by LeMoult *et al.*

(2020) suggests that early-life stress increases MDD risk early in development. Multiple studies have linked early-life stress with increased inflammation (Danese and Lewis 2017). For example, males with current MDD and a history of high early-life stress exhibited significantly greater increases in IL-6 and nuclear factor (NF)-kB DNA binding following a psychosocial stressor compared with nondepressed male control subjects (Pace *et al.* 2006).

It has been suggested that an important and relatively underappreciated mechanism for the link between depression and inflammatory disorders may be disruption of the immunoregulatory balance between pro-and antiinflammatory cytokines (Dhabhar *et al.* 2009). The cytokine balance can be tilted toward a proinflammatory milieu because of elevated concentrations of inflammatory cytokines such as IL-6, lowered concentrations of antiinflammatory/immunomodulatory cytokines such as IL-10, or a combination of the two. Therefore, in addition to the absolute concentrations of these cytokines, the relative concentrations of pro-and antiinflammatory cytokines can provide a useful index of the net inflammatory milieu and of immune dysregulation. In keeping with this hypothesis, it has been demonstrated that in comparison with control subjects, depressed subjects manifest significantly lower serum IL-10 concentrations, nonsignificantly higher IL-6 concentrations, and significantly higher IL-6 to IL-10 ratios (Dhabhar *et al.* 2009). Furthermore, higher levels of depressive

symptoms were significantly related to lower IL-10 concentrations and tended to be related to higher IL-6 to IL-10 ratios but were not significantly related to IL-6 concentrations across the total sample of participants (Dhabhar *et al.* 2009). Moreover, control subjects showed a strong positive correlation between serum IL-6 and IL-10 concentrations, which was completely absent (near-zero effect size) in depressed subjects. Although depressed subjects had significantly higher BMIs than did the controls, covarying for BMI (or controlling for BMI) did not alter this finding (Dhabhar *et al.* 2009).

Given the antiinflammatory properties of glucocorticoids (Rhen and Cidlowski 2005), it might be expected that patients with depression who have decreased glucocorticoid sensitivity, as manifested by nonsuppression of cortisol on the dexamethasone suppression test (DST), would be especially likely to show signs of immune activation. Some evidence suggests that this is indeed the case. Compared with patients with depression who have normal in vivo glucocorticoid sensitivity, patients who are DST nonsuppressors show increased plasma concentrations of the acute-phase reactant a_1-glycoprotein, as well as increased in vitro mitogen-stimulated IL-6 production (Pace and Miller 2009; Sluzewska 1999).

Other Psychiatric Disorders and Immune Function

Evidence suggests that other stress-related neuropsychiatric conditions--including anxiety disorders, schizophrenia, PTSD, chronic fatigue syndrome, seasonal affective disorder, and fibromyalgia--may also be associated with immune activation and neuroinflammation (Chauhan *et al.* 2021; Dziabis and Bilbo 2022; Feng *et al.* 2020; Fonken *et al.* 2018; Heurich *et al.* 2022; Liu and Quan 2018), although these conditions have been less well characterized than MDD. Individuals with combat-related PTSD have been reported to demonstrate increased plasma concentrations of IL-1, increased CSF concentrations of IL-6, and increased expression of genes related to inflammation and NF-kB systems (Yang and Jiang 2020). PTSD following civilian disasters appears to be associated with elevated plasma concentrations of IL-6 and its soluble receptor (Maes *et al.* 1999b). PTSD following childhood abuse is associated with enhanced CMI responses (Altemus *et al.* 2003). Although they have not been found consistently (Maes *et al.* 1999b), both severity of symptoms and duration of illness have been reported to correlate positively with indices of immune activation in PTSD (R. Miller *et al.* 2001; Spivak *et al.* 1997).

A growing body of literature suggests that patients exposed to early-life trauma may be especially vulnerable to the development of psychophysical disorders (e.g., chronic fatigue syndrome, fibromyalgia) that are characterized by complaints of chronic pain, fatigue, and cognitive difficulties of unknown etiology (Heim *et al.* 1997). Consistent with this vulnerability, these disorders have also been associated with evidence of increased inflammatory activity. For example, it has been reported that both chronic fatigue syndrome and fibromyalgia are accompanied by an increase in acute-phase reactants and increased plasma concentrations and/or peripheral blood mononuclear cell production of proinflammatory cytokines, including IL-1, IL-6, and TNF-a (Borish *et al.* 1998; Cannon *et al.* 1999; Gupta *et al.* 1997; Maes *et al.* 1999a). Of note, one report indicates that seasonal affective disorder, a condition with significant symptom overlap with chronic fatigue syndrome and fibromyalgia, may be characterized by increased plasma concentrations of IL-6 (Leu *et al.* 2001).

Finally, there has been speculation that immune system activation may contribute to the pathophysiology of psychotic disorders, including schizophrenia, possibly related to an autoimmune diathesis (Pearce 2001; Rothermundt *et al.* 2001). Elevated levels of cytokines and their receptors, including IL-2, soluble IL-2, TNF, and IL-6, have been reported in the blood and CSF of patients with schizophrenia (Goldsmith *et al.* 2016), and a high level of CSF IL-2 has been found to predict subsequent schizophrenic relapse (Rothermundt *et al.* 2001). In a related fashion, on the basis of seasonal birth patterns that have been reliably replicated in large epidemiological studies of patients with schizophrenia, consideration has been given to the role of viral infection early in development (Pearce 2001). These findings are consistent with in utero infections of relevant brain structures, including the hippocampus, during critical periods of development (especially during the second trimester) (Pearce 2001). Moreover, cross-reactivity between brain antigens and antigens of infectious agents may contribute not only to schizophrenia but also to the neurological and psychiatric complications associated with streptococcal infection (i.e., pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections [PANDAS]) (Snider and Swedo 2000). Finally, microglial activation is reported to be involved in the context of schizophrenia (Izuo and Nitta 2021) and autism (Bilbo *et al.* 2018), and it has been suggested that immune mechanisms involving activation of the complement system and microglia contribute to psychiatric disorders by mediating synaptic dysfunction and/or loss (Stevens and Johnson 2021; Tenner *et al.* 2018).

Mediating Pathways

Underlying the ability of the CNS to affect the immune system is a host of connections between autonomic nervous system (ANS) and neuroendocrine pathways and immune system elements. Immune cells are able to directly respond to brain outflow pathways via receptors for small-molecule neurotransmitters, adrenal and gonadal steroids, hypothalamic-releasing factors, and other neuropeptides (Raison *et al.* 2002). Specific receptor densities vary among immune cell types, and these variations correlate with cell sensitivity to a given ligand.

Autonomic Nervous System

It is well known that sympathetic and parasympathetic pathways within the ANS interact to maintain homeostasis in a variety of physiological states, including regulation of the immune response. In addition to expressing receptors for autonomic and neuroendocrine signaling molecules, immune cells and tissues are innervated by fibers derived from the ANS, together forming a neural pathway that can reflexively regulate the immune response (Czura *et al.* 2007; Downing and Miyan 2000; Miller 1998; Raison *et al.* 2002; Sanders and Kavelaars 2007; Tracey 2002). The sympathetic branch of the ANS appears able to influence the immune system either by changing the vascular tone and blood flow into lymphoid organs or by directly influencing immune cell function via locally released neurotransmitters, especially norepinephrine, and neuropeptides such as neuropeptide Y, substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and CRH, which, in turn, interact with specific receptors on nearby immune cells (Bellinger *et al.* 1997; Czura *et al.* 2007).

In addition to immune regulation by the sympathetic branch, the parasympathetic branch of the ANS has been shown to contribute to the regulation of innate immune responses via an efferent neural signaling pathway referred to as the *cholinergic antiinflammatory pathway* (Tracey 2002). The existence of this pathway was initially identified in studies showing that stimulation of the vagus nerve attenuates immune system activation and the physiological signs of septic shock in response to lipopolysaccharide, a key component of gram-negative bacterial cell walls (Borovikova *et al.* 2000). Follow-up studies have determined that vagal release of acetylcholine, which in turn interacts with the a7 subunit of the acetylcholine receptor (a7nAChR) on relevant immune cells, is capable of suppressing production of cytokines, including TNF-a, via inhibitory effects on nuclear translocation of NF-kB (Altavilla *et al.* 2006; Guarini *et al.* 2003) and activation of JAK2 (Janus kinase 2)/STAT3 (signal transducer and activator of transcription 3) (de Jonge *et al.* 2005; Pavlov and Tracey 2005).

Subsequent investigations have established that cytokine production is inhibited by efferent vagal pathways in the context of a variety of inflammatory processes, including myocardial ischemia, hemorrhagic shock, ischemia/reperfusion, and pancreatitis (Altavilla *et al.* 2006; Guarini *et al.* 2003; Mioni *et al.* 2005; van Westerloo *et al.* 2006; Wang *et al.* 2004). It also has been shown that both vagus nerve stimulation and a7nAChR agonists inhibit production of a number of proinflammatory cytokines, including TNF, IL-1, IL-6, IL-8, and high-mobility group box 1 (Wang *et al.* 2004). Notably, a specific a nAChR-dependent vagus nerve pathway to the spleen has been identified that inhibits proinflammatory cytokine production during endotoxemia and polymicrobial sepsis. Furthermore, both splenectomy and vagotomy interrupt the cholinergic antiinflammatory response (Huston *et al.* 2006). Interestingly, on the basis of these findings, electrical stimulation by vagal afferents has been designated as a breakthrough treatment by the FDA for the treatment of rheumatoid arthritis (Pavlov *et al.* 2020). Of note, vagal nerve stimulation used to treat depression provides only efferent vagal nerve stimulation, although in a recent study, transcutaneous vagal nerve stimulation was found to decrease IL-6 and IFN-g in patients with PTSD (Bremner *et al.* 2020). Taken together, these findings suggest that in addition to effects on cellular signaling, there are anatomical and hard-wired components of the cholinergic antiinflammatory pathway that may have therapeutic relevance.

Hypothalamic-Pituitary-Adrenal Axis

In concert with the ANS, the HPA axis serves as a central component of the mammalian stress response system. Although glucocorticoids, which represent the final product of HPA axis activation, have long been viewed as immunosuppressive because of their well-documented ability to suppress inflammation (largely through protein-protein interactions between the glucocorticoid receptor and NF-kB) (Rhen and Cidlowski 2005), it is increasingly recognized that HPA axis effects on immunity are complex (Dhabhar 2009a, 2009b, 2014; Dhabhar *et al.* 1995). This complexity arises from the fact that HPA axis effects on the immune system depend on numerous factors, including the immune compartment that is being assessed, the element of the HPA axis being evaluated (i.e., CRH vs. cortisol), and the duration and timing relative to the immune response and stressor application. Thus, for example, glucocorticoids are known to mediate immune cell redistribution in the body (Dhabhar *et al.* 1996, 2012) and to enhance CMI in vivo (Dhabhar and McEwen 1996) through their effects on lymphocyte trafficking (Dhabhar 1998, 2009a, 2014). Moreover, different HPA axis elements demonstrate divergent immune system effects. For example, the end result of CRH-induced HPA axis activation is proinflammatory cytokine suppression, yet studies demonstrate that the direct effect of CRH on proinflammatory cytokine production may be stimulatory (Labeur *et al.* 1995; Paez Pereda *et al.* 1995).

Finally, the effect of glucocorticoids on naturalistic measures of immunity, such as cutaneous CMI, depends on both the concentration and the duration of glucocorticoids within the immune compartment under consideration. Thus, low doses of glucocorticoids applied for brief periods have been shown in rodents to stimulate CMI, whereas higher (or more protracted) glucocorticoid exposure suppresses CMI (Dhabhar 2009a, 2009b, 2014; Dhabhar and McEwen 1999).

CRH applied within the CNS suppresses several measures of immunity, including splenic NK cell activity, mitogen-stimulated lymphocyte proliferation, and in vivo and in vitro antibody formation, as well as T cell responses to T cell receptor antibody (Caroleo *et al.* 1993; Irwin *et al.* 1988; Labeur *et al.* 1995; Rassnick *et al.* 1994). In contrast to its immunosuppressive properties, CRH has also been shown to enhance proinflammatory cytokine production in rodents and humans when administered peripherally or within the CNS. Chronic intracerebroventricular administration of CRH to rats leads to induction of IL-1b messenger RNA (mRNA) in splenocytes, and acute intravenous administration in humans has been reported to cause a fourfold increase in the induction of IL-1a (Labeur *et al.* 1995; Schulte *et al.* 1994). In addition to potential proinflammatory activities of CRH within the CNS, peripheral production of CRH has been demonstrated in inflammatory diseases such as ulcerative colitis and arthritis, in which it appears to act as a local proinflammatory agent (Karalis *et al.* 1997; Nishioka *et al.* 1996).

Of all neurotransmitters or hormones known to modulate immune functioning, the actions of glucocorticoids, although complicated, are probably the best understood (Raison *et al.* 2002). Identified effects of glucocorticoids on the immune (and inflammatory) system include the following:

- Modulation of immune cell trafficking throughout the body (Dhabhar *et al.* 1995)
- Enhancement of CMI by physiological concentrations of endogenous glucocorticoids (Dhabhar 2009a, 2009b, 2014; Dhabhar and McEwen 1999)
- Promotion of Th2 (antibody) responses (Elenkov and Chrousos 1999)
- Modulation of cell death (i.e., apoptosis) pathways (McEwen *et al.* 1997)
- Inhibition of arachidonic acid pathway products (e.g., prostaglandins) that mediate inflammation and illness symptoms (e.g., fever) (Goldstein *et al.* 1992)
- Inhibition of T cell-and NK cell-mediated cytotoxicity (Raison *et al.* 2002)
- Inhibition of cytokine production and function through interaction of glucocorticoid receptors with transcription factors (NF-kB in

particular), which in turn regulate the expression of cytokine genes and/or cytokine-inducible genes (McKay and Cidlowski 1999)

Although glucocorticoids may actually enhance certain aspects of naturalistic immune functioning when produced for brief periods at low to moderate doses in the context of acute and/or mild stress, glucocorticoids in general play a primary role in restraining excessive or prolonged inflammatory activation (Munck 1989). This property has long been exploited by modern medicine for the treatment of autoimmune and other chronic inflammatory conditions, with the result that glucocorticoids remain a cornerstone of our antiinflammatory armamentarium. Consistent with their pharmacological uses, glucocorticoids have been shown to be essential for inflammatory regulation in response to immune system activation. For example, neutralization of endogenous glucocorticoid function results in increased pathology and mortality in rodents exposed to lipopolysaccharide or to other inflammatory stimulators such as streptococcal cell wall antigen or myelin basic protein (Bertini *et al.* 1988; Sternberg *et al.* 1989). Similarly, rodents that have been rendered glucocorticoid deficient by adrenalectomy have markedly increased death rates following infection with murine CMV, an effect that arises from unrestrained activity of the proinflammatory cytokine TNF (Ruzek *et al.* 1999). Relevant to chronic stress, increased inflammatory cytokines can also disrupt translocation of the glucocorticoid receptor from cytoplasm to the nucleus, leading to glucocorticoid resistance (Pace and Miller 2009).

Effects of the Immune System on the Brain and Behavior

Immune System-to-Brain Signaling Pathways

The field of psychoneuroimmunology is based on the existence of bidirectional communication pathways between the nervous and immune systems (Ader 2007; Miller *et al.* 2000). This bidirectionality implies that just as the CNS is capable of modulating immunity, the immune system can alter functioning within the CNS. Although researchers historically were interested in pathways by which the brain affects immunity, the past 20-30 years have seen a groundswell of interest in the ways in which the immune system contributes to the development of psychopathology (Capuron and Miller 2011; Steinberg *et al.* 2015).

Underpinning this growing interest is an increasing appreciation for the multiple ways in which inflammatory cytokines are able to signal the brain and change CNS function (Table 5-2). Although the brain was initially considered an "immune privileged" organ, protected from immune system activity by the blood-brain barrier, it is now clear that cytokines released in the periphery rapidly affect CNS functioning via multiple pathways (see Table 5-2) (Banks 2006; Banks *et al.* 1995; Maier *et al.* 1998; Plotkin *et al.* 1996; Quan 2006, 2014; Raison *et al.* 2002; Rivest *et al.* 2000). Moreover, immune cells are now known to patrol the brain through lymphatic vessels and the meninges, and increasing data indicate that the brain represents an immune system compartment that generates its own local immune environment, which serves as the backdrop for peripheral immune influences (Cugurra *et al.* 2021; Rustenhoven *et al.* 2021).

TABLE 5-2. **Evidence that cytokines can alter central nervous system function**

1. Cytokines released peripherally have access to the brain.
   * Passage through leaky regions or disruptions in the blood-brain barrier during stress
   * Active transport
   * Activation of intermediary cell types (e.g., endothelial cells) that produce relevant second messengers (e.g., prostaglandins, reactive nitrogen and oxygen species, cytokines)

    - * Transmission of cytokine signals through afferent nerve fibers (e.g., vagus)
    - * Entry of immune cells into the brain parenchyma
2. A cytokine network exists within the brain.
    - * Glia (especially microglia) and neurons express/produce cytokines and express cytokine receptors
    - * The glymphatic system allows local access by immune mediators to brain regions, especially those in proximity to the CSF.
3. Cytokines have effects on neurotransmitter turnover, neuroendocrine function, synaptic plasticity, neurocircuitry, and behavior.

Once inflammatory cytokine signals gain access to the CNS, the signal is amplified by a cytokine network within the brain itself (Quan *et al.* 1999). Receptors for inflammatory cytokines are found throughout the brain, especially in subcortical regions including the striatum, which play a pivotal role in integrating neurotransmitter inputs that regulate motivation and motor activity, but also including the insula, dorsal anterior cingulate cortex (dACC), amygdala, hippocampus, and hypothalamus, which

play important roles in emotion regulation and homeostasis. Among neural cells, activated microglia are capable of producing inflammatory cytokines and nitrogen and oxygen radicals, which in turn are potent activators of other glial elements including astrocytes and oligodendrocytes (Miller and Raison 2016; Schobitz *et al.* 1994). Of interest, growing evidence suggests that nonimmunological stressors can also induce cytokine expression in the brain, an effect likely mediated by stress-induced activation of microglia in part related to reduced neuronal production of fractalkines that regulate reactive microglia (Frank *et al.* 2007; Weber *et al.* 2017). These data suggest that CNS cytokine pathways may participate in an organism's response to a wide variety of environmental perturbations.

Inflammation and Depression

A rich database indicates that inflammation may play a role in the development of multiple psychiatric disorders, including MDD, which has been the most studied in this regard (Beurel *et al.* 2020; Miller and Raison 2016). As noted earlier in this chapter, patients with MDD exhibit all the cardinal features of a chronic inflammatory response, including increases in peripheral blood and CSF inflammatory cytokines, acute-phase reactants, chemokines, and cellular adhesion molecules. Meta-analyses of this literature indicate that peripheral blood concentrations of IL-6, IL-1, and TNF, along with CRP, are the most reliably elevated in this regard (Dowlati *et al.* 2010; Howren *et al.* 2009). In addition, there is evidence of increased inflammation in the brain, as reflected by increased inflammatory signaling molecules such as toll-like receptors in brain parenchyma (Pandey 2017), activation of microglia, and evidence of immune cell trafficking to brain perivascular regions and the meninges (Miller and Raison 2016; Setiawan *et al.* 2015; Torres-Platas *et al.* 2014). A second major body of data that indicates that there is a link between inflammation and depression is that the administration of inflammatory cytokines such as interferon-a (IFN-a) (used for the treatment of cancer and infectious diseases), as well as inflammatory stimuli, including endotoxin and typhoid and influenza vaccinations (typically given to healthy volunteers), leads to the development of depressive symptoms (Miller and Raison 2016; Miller *et al.* 2013). Moreover, inhibition of inflammation can reduce depressive symptoms. These latter findings are most apparent in patients with autoimmune and inflammatory disorders administered anticytokine therapies (Kappelmann *et al.* 2018), although, as indicated below, there is some evidence that antiinflammatory drugs, including anticytokine therapies, may reduce depressive symptoms in patients with depression who are otherwise medically healthy (Kohler-Forsberg *et al.* 2019). Additional evidence of a relationship between inflammation and depression is the observation that rates of depression are significantly elevated in a wide variety of medical conditions, including inflammatory and autoimmune disorders such as multiple sclerosis and rheumatoid arthritis, as well as in illnesses such as cardiovascular disease, diabetes, and cancer, which are increasingly being recognized as having an inflammatory component (Aggarwal *et al.* 2006; Blake and Ridker 2002; Currier and Nemeroff 2014; Dantzer *et al.* 2008, 2011; Evans *et al.* 2005). Finally, increased inflammatory markers, including CRP and IL-6, have been found to reliably predict the development of depression in longitudinal studies (Mac Giollabhui *et al.* 2020; Raison *et al.* 2006).

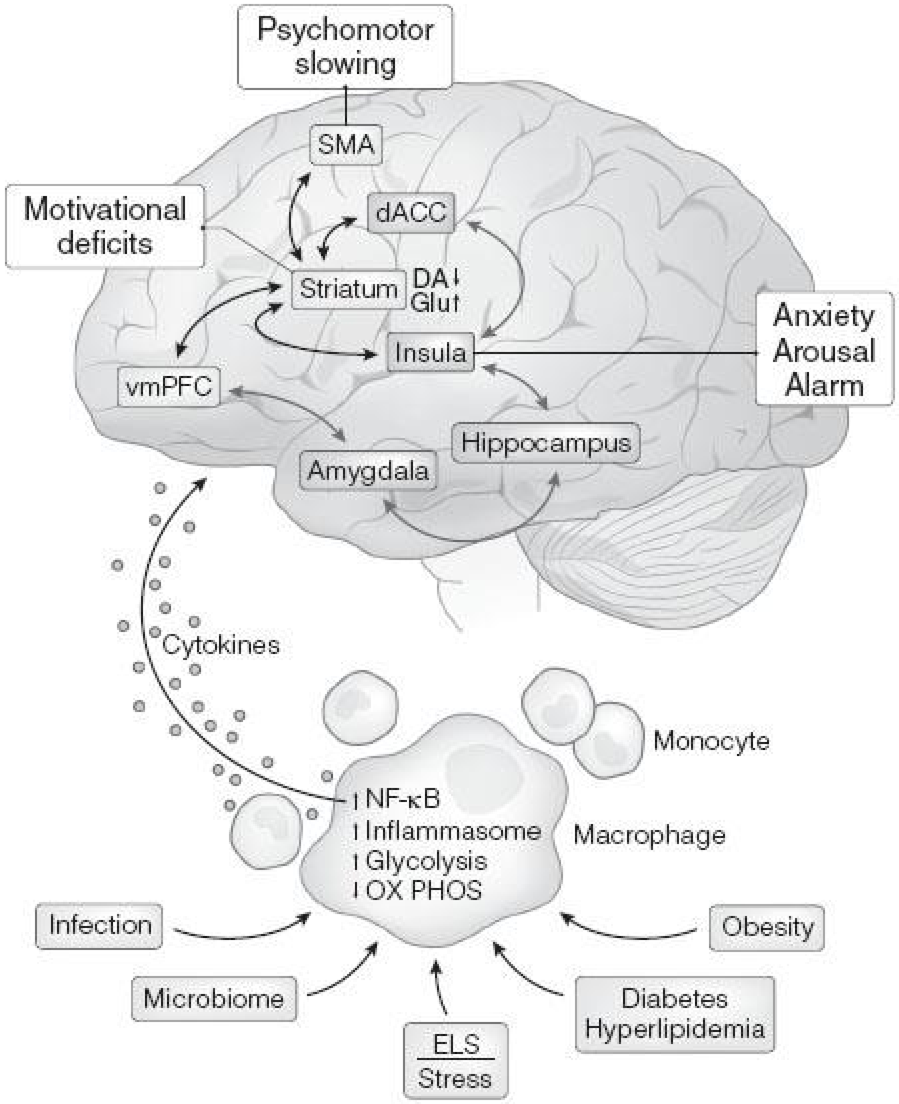
It should be noted that psychiatric disorders such as depression are not inflammatory disorders per se, and inflammation is increased only in a subgroup of depressed patients (approximately 30% depending on the sample) (Osimo *et al.* 2019). The relative presence of inflammation is determined in part by other mitigating factors that can drive inflammatory responses, including obesity, stress (especially early-life stress), older age, chronic medical illnesses, dysbiosis, infection, and trauma (Lucido *et al.* 2021). Moreover, as mentioned earlier in this chapter, increased inflammation in association with behavioral changes is seen in multiple psychiatric disorders, including mood disorders, anxiety disorders, PTSD, and schizophrenia (Goldsmith *et al.* 2016). In general, based on our understanding of the effects of inflammation on the brain and behavior, inflammation-induced behavioral changes are not specific to any one disorder. Indeed, they are agnostic to diagnosis and truly transdiagnostic in nature (Lucido *et al.* 2021). As described below, inflammation leads to relatively specific effects on neurotransmitter systems, neurocircuits, and ultimately symptoms across disorders.

Pathways by Which Inflammation Produces Depression and Neuropsychiatric Disturbance

Given the substantial amount of data indicating that inflammation and depression have a cause-and-effect relationship (as evidenced by the induction of depressive symptoms by inflammatory stimuli and the reversal of depressive symptoms by antiinflammatory drugs in patients with increased inflammation), much attention has been paid to the potential mechanisms involved. Research to date has provided convincing evidence that the impact of inflammation on the brain is mediated through effects on the neurotransmitter systems and neurocircuits that are involved in behaviors reliably associated with depressive disorders, including alterations in motivation and motor activity as manifested by anhedonia and psychomotor retardation, as well as symptoms of anxiety, arousal, and alarm (Miller *et al.* 2013) (Table 5-3; Figure 5-2).

TABLE 5-3. Potential mechanisms by which cytokines may influence behavior

Alteration of monoamine and glutamate metabolism
Inhibition of relevant growth factors and neuroplasticity
Disruption of neurocircuitry mediating reward processing and threat sensitivity
Dysregulation of glucose and lipid metabolism and activation of the kynurenine pathway


Psychomotor slowing
SMA
Motivational deficits
dACC
Striatum
DA↓
Glu↑
Insula
Anxiety
Arousal
Alarm
vmPFC
Hippocampus
Amygdala
Cytokines
Monocyte
↑NF-κB
↑Inflammasome
↑Glycolysis
↓OX PHOS
Macrophage
Infection
Obesity
Microbiome
Diabetes
Hyperlipidemia
ELS
Stress

Art credit: Katie Vicari

FIGURE 5-2. Pathophysiological pathways from inflammation to the brain and behavior.

Multiple predisposing factors including early-life stress (ELS), metabolic derangements, infection, and illness can drive inflammatory signaling pathways involving nuclear factor kB (NF-kB) and the inflammasome in immune cells such as monocytes, which in turn undergo metabolic reprogramming, including a shift from oxidative phosphorylation (OX PHOS) to glycolysis. Activated immune cells (e.g., macrophages) then produce inflammatory cytokines that access the brain and influence neurotransmitter systems, including dopamine (DA) and glutamate (Glu), in the striatum, thereby disrupting functional connectivity of the striatum to the ventromedial prefrontal cortex (vmPFC) and supplementary motor area (SMA). These effects on neurocircuitry lead to behavioral alterations such as decreased effort-based motivation, anhedonia, and psychomotor slowing. Inflammatory cytokines can also engage neurocircuits involving the dorsal anterior cingulate cortex (dACC), insula, hippocampus, and amygdala, leading to behavioral states characterized by anxiety, arousal, and alarm.

Source. Created by Katie Vicari (www.KatieRisVicari.com). Used with permission.

Effects of Inflammation on Monoamine Neurotransmitters, Glutamate, and Growth Factors

Inflammatory mediators, including inflammatory cytokines, have been shown to decrease the synthesis and release and increase the reuptake of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine. Regarding synthesis, inflammation has been shown to decrease the availability of tetrahydrobiopterin (BH4), which is an essential enzyme cofactor for all of the enzymes responsible for the synthesis of the monoamines as well as nitric oxide (NO) synthase (Felger *et al.* 2013a; Haroon *et al.* 2012). In the context of inflammation and activation of NO synthase, BH4 is converted to BH2 in the production of NO, which plays a pivotal role in pathogen clearance and wound healing. Studies in humans with increased inflammation have shown decreased BH4 activity as manifested by an increase in the phenylalanine-to-tyrosine ratio, given the role of BH4 in supporting the activity of phenylalanine hydroxylase, the enzyme that converts phenylalanine to tyrosine (Felger *et al.* 2013a). In addition, in patients treated with IFN-a, an increase in the phenylalanine-to-tyrosine ratio was found in association with depressive symptoms and decreased CSF dopamine, and decreased CSF BH4 was associated with increased CSF IL-6 (Felger *et al.* 2013a). Interestingly, the conversion of BH2 to BH4 can be promoted by folic acid, L-methylfolate, and *S*-adenosyl methionine (SAMe), and L-methylfolate was found to be effective in the treatment of antidepressant nonresponders, but only those with evidence of increased inflammation and BMI at baseline (Shelton *et al.* 2015). In terms of monoamine release, studies in laboratory animals have reliably demonstrated that inflammatory cytokines can decrease the release of dopamine in the striatum in association with reduced effort-based motivation (Felger *et al.* 2013b). Of note, no effects were found in the ability to experience pleasure, which is primarily mediated by opioid signaling pathways. The mechanism of these effects on monoamine release remains unclear, although there is some evidence that effects on the vesicular monoamine transporter may be involved. Finally, inflammatory cytokines including TNF and IL-1b have been shown to increase both expression and function of monoamine reuptake transporters, leading to decreased monoamine availability in the synapse, which in turn has been associated with depressive-like behaviors in rodents exposed to endotoxin (Zhu *et al.* 2010).

Another major neurotransmitter affected by inflammation is glutamate. Glutamate is the major excitatory neurotransmitter in the brain, and its concentration is carefully controlled to avoid toxicity and local and regional brain dysfunction (Haroon *et al.* 2017). Inflammatory mediators, including inflammatory cytokines, have well-established effects on astrocytes that lead to a buildup of synaptic glutamate, including decreasing the excitatory amino acid transporters that remove glutamate from the synapse and inducing reverse efflux of glutamate from these transporters, leading to increased release of glutamate from the xC transporter in the process of producing glutathione to combat inflammation-induced oxidative stress (Haroon *et al.* 2017). These effects can lead to excessive synaptic glutamate that can spill over into the extrasynaptic space and bind to extrasynaptic glutamate receptors, which can lead to decreased production of growth factors such as brain-derived neurotrophic factor (BDNF) and ultimately excitotoxicity (Haroon *et al.* 2017). Of note, inflammation--including IL-1b and its signaling pathway NF-kB--has been shown to have direct effects on BDNF production and neurogenesis (Koo *et al.* 2010). Activated microglia can also produce glutamate, further exacerbating the impact of inflammation on glutamate regulation (Haroon *et al.* 2017). Studies using magnetic resonance spectroscopy in humans receiving IFN-a or depressed patients manifesting increased inflammation have demonstrated increased glutamate in the dACC and basal ganglia (including striatum) in association with disruption in the coherence and precision of local neuronal firing and functional connectivity throughout the brain as well as behavioral changes including anhedonia and treatment nonresponse (Haroon *et al.* 2014, 2016, 2018a).

Taken together, inflammatory cytokines can reduce monoamine availability and increase glutamate while reducing BDNF and neurogenesis, leading to depression. These effects may in turn undermine treatment response to conventional antidepressants, whose efficacy relies on increasing synaptic monoamines and increasing BDNF-induced neurogenesis, while having no substantial effect on glutamate, thereby contributing to antidepressant treatment resistance (see subsection "Treatment Implications of Inflammation Effects on the Brain" below) (Raison *et al.* 2013a).

Effects of Inflammation on Neurocircuitry

In conjunction with studies examining the impact of inflammation on neurotransmitter systems and growth factors in the brain, a variety of neuroimaging strategies have been used to examine the impact of inflammation on neurocircuitry. Studies have included those in which subjects are exposed to inflammatory stimuli, as well as a smaller number of studies examining the relationship between endogenous inflammation and brain neurocircuitry. In general, two major targets of inflammation have been reliably characterized: subcortical (striatum) and prefrontal cortical brain regions involved in motivation and motor activity, and threat circuitry involving the amygdala, insula, dACC, and hippocampus (Miller and Raison 2016; Miller *et al.* 2013). For example, in separate studies conducted in independent laboratories, IFN-a, endotoxin, and typhoid vaccination have all been found to decrease activation of the ventral striatum in association with depressive symptoms, including decreased motivation (Capuron *et al.* 2012; Eisenberger *et al.* 2010; Harrison *et al.* 2016). Of note, the ventral striatum is the same brain region where reliable inflammation-induced decreases in dopamine and increases in glutamate were observed, and these two neurotransmitters are well known for their role in reward processing and motor activity (Felger *et al.* 2013b; Haroon *et al.* 2016). In addition, increased endogenous inflammation as reflected by elevated CRP has been shown to correlate with reduced functional connectivity between the ventral striatum and the ventromedial prefrontal cortex in conjunction with anhedonia. Increased endogenous inflammation has also been associated with reduced functional connectivity involving dorsal striatal regions in relation to decreased psychomotor speed (Felger *et al.* 2016). Regarding threat circuitry, a recent study showed increased amygdala reactivity following IFN-a administration to patients with hepatitis C and decreased amygdala reactivity following administration of infliximab to patients with autoimmune and inflammatory disorders (Davies *et al.* 2020). Several studies have also shown increased activation of the dACC in association with inflammation and hypersensitivity to social threat and error processing (Capuron *et al.* 2005; Slavich *et al.* 2010). Although potentially contributing to psychiatric symptoms in modern times, these effects of inflammation on motivation and motor activity as well as arousal, anxiety, and alarm are believed to have subserved survival priorities in ancestral times to allow conservation of energy resources for fighting infection and wound healing (via reduced exploratory activity) as well as provoking hypervigilance to protect a wounded or infected defenseless animal from attack (Raison and Miller 2013).

Effects of Inflammation on Glucose and Lipid Metabolism, the Kynurenine Pathway, and Glucocorticoid Receptor Function

Additional pathways, including the metabolism of glucose and lipids as well as activation of the kynurenine pathway, appear to contribute to the effects of inflammation on behavior. In terms of cellular metabolism, there has been increasing interest in the role of immune cell metabolism, or immunometabolism, as an important mechanism related to the impact of inflammation on the brain (Treadway *et al.* 2019). Indeed, when immune cells become activated, they shift their metabolism from the energy-efficient oxidative phosphorylation to the energy-inefficient glycolysis. This so-called Warburg effect puts a marked energy demand on the body, and in the context of immune activation, inflammation can account for up to 30% of the daily energy expenditure, greatly reducing the energy available for other activities (Straub 2017). Interestingly in this regard, anhedonia, specifically the unwillingness to expend effort for reward, in depressed patients with increased inflammation is associated with activation of signaling pathways associated with glycolysis, suggesting that both a metabolic shift toward glycolysis and inflammation, in some combination, are involved in the expression of anhedonia (Bekhbat *et al.* 2020). In a related fashion, the treatment response to the TNF antagonist infliximab is predicted by gene expression pathways overrepresented by gluconeogenesis and lipid metabolism, and treatment responders to infliximab exhibit decreased plasma lipids following infliximab administration (Bekhbat *et al.* 2018; Mehta *et al.* 2013). Similar results have been found with symptoms of psychomotor retardation (Bekhbat *et al.* 2021), and in patients with depression, markers of impaired glucose metabolism are associated with decreased functional connectivity between the ventral striatum and ventromedial prefrontal cortex, but only in patients with high inflammation (Goldsmith *et al.* 2020). Motivational deficits and negative symptoms in patients with schizophrenia are also associated with increased plasma lipids, but only in patients with high inflammation (Goldsmith *et al.* 2021). Taken together, these data suggest that there is an interaction between metabolic shifts in both cellular and systemic immunometabolism and inflammation that leads to behavioral changes related to motivation and motor activity.

The kynurenine pathway has also been implicated as a potential mediator of the effects of inflammation on the brain and behavior. Inflammatory stimuli, including TNF and IFN-g, activate the enzyme indoleamine 2,3 dioxygenase (IDO) in monocytes and dendritic cells (Haroon *et al.* 2020). Upon activation, IDO converts tryptophan

to kynurenine, which can be transported to the brain by the large neutral amino acid transporter (Haroon *et al.* 2020). Once in the brain, kynurenine is converted to kynurenic acid by astrocytes and quinolinic acid by microglia. Quinolinic acid can bind to extrasynaptic *N*-methyl-D-aspartate receptors, leading to excitotoxicity. Quinolinic acid can also cause astrocytes to increase release and decrease reuptake of glutamate, further contributing to excessive glutamate as a result of inflammation (Haroon *et al.* 2020). Activation of the kynurenine pathway as evidenced by an increased kynurenine-to-tryptophan ratio has been associated with increased glutamate in the basal ganglia as well as decreased regional homogeneity and functional connectivity in multiple brain regions in association with anhedonia and treatment nonresponse (Chen *et al.* 2021). Interestingly, competitive blockade of the large neutral amino acid transporter by leucine following administration of endotoxin has been shown to abrogate depressive-like behavior in mice (Walker *et al.* 2019). These data indicate that the kynurenine pathway may be a relevant target for treatment development in individuals with increased inflammation. Of note, there appears to be a special relationship between activation of the kynurenine pathway and suicide, suggesting that such treatment development may be particularly relevant for psychiatric patients with increased inflammation and suicidal ideation (Brundin *et al.* 2016).

Although there are homeostatic regulatory mechanisms available in the body to modulate inflammatory responses, one of the most potent of these, glucocorticoids, are rendered ineffective by the effects of inflammation on the glucocorticoid receptor. Indeed, as noted above, inflammatory cytokines have been shown to decrease the translocation of the glucocorticoid receptor from cytoplasm to nucleus through activation of p38 MAPK (mitogen-activated protein kinase) signaling pathways. Other inflammatory signaling pathways--including NF-kB, Jun amino (N)-terminal kinase (JNK), and STAT5--have also been shown to alter glucocorticoid receptor function (Pace *et al.* 2007). Thus, inflammatory cytokines can contribute to a state of glucocorticoid resistance, which has been well described in depressed patients and can lead to a feedforward cascade of stress and inflammation in depression and other psychiatric disorders, including anxiety disorders and PTSD.

Treatment Implications of Inflammation Effects on the Brain

Given the detailed understanding of how inflammation can influence the brain to change behavior, there has been considerable interest in testing antiinflammatory drugs in the populations of patients that exhibit increased inflammation. The majority of studies have included patients with depression as well as patients with schizophrenia. While the results provide some promise of modest effects, there are a number of limitations of the clinical trials that have been conducted to date, complicating the interpretation of the findings.

A number of medications with antiinflammatory properties have been explored in depression and schizophrenia, including cytokine antagonists; cyclooxygenase inhibitors such as aspirin and other nonsteroidal antiinflammatory drugs; minocycline, a microglial stabilizer and antibiotic; statins; glucose-lowering drugs such as pioglitazone; omega-3 fatty acids; and glucocorticoids. Meta-analyses of this literature indicate that these medications are generally well tolerated and provide modest improvement in depressive symptoms (Kohler-Forsberg *et al.* 2019). However, many of the trials were of small size, and few targeted patients with increased inflammation specifically. Given that only about one-third of depressed patients exhibit increased inflammation, these findings should be interpreted with caution. Indeed, the largest trial to date, which included depressed patients treated with minocycline, the cyclooxygenase inhibitor celecoxib, or placebo, showed no difference among or between treatment groups (Husain *et al.* 2020). As with other trials, however, this study did not stratify patients on the basis of inflammatory status. Population-based studies examining much larger sample sizes have failed to find reliable efficacy of antiinflammatory agents, largely cyclooxygenase inhibitors, in preventing depression (Berk *et al.* 2020). Nevertheless, one large study in cancer patients did see a significant effect of aspirin in reducing depressive symptoms (Hu *et al.* 2020). Of note, cancer patients are well known to exhibit increased inflammation by virtue of their cancer and its treatment. In terms of schizophrenia, meta-analyses examining the effects of celecoxib and minocycline have revealed evidence of safety and modest efficacy as an adjunct to antipsychotic therapy (Xiang *et al.* 2017). Nevertheless, as with similar studies in depression, sample sizes were small, and the patients were not selected based on inflammatory status. Taken together, the data on antiinflammatory agents for depression and schizophrenia, while promising, are difficult to interpret given the clinical trial designs and the limited sample sizes. These limitations will be discussed in more detail below.

Another important translational observation regarding the impact of inflammation on the treatment of psychiatric disease is that increased inflammation is associated with treatment nonresponse, especially in patients with MDD. Increased inflammatory biomarkers prior to antidepressant treatment predict treatment nonresponse (Strawbridge *et al.* 2015), and depressed patients who have failed to respond to multiple antidepressant treatment trials are more likely to exhibit increased inflammatory markers (Haroon *et al.* 2018b). Furthermore, many of the clinical predictors of poor response to antidepressant treatment, including obesity, childhood maltreatment, anxiety disorders, PTSD, and OCD, have been associated with increased inflammatory biomarkers (Miller *et al.* 2009). Interestingly, increased inflammatory biomarkers, including IL-6, have been shown to predict response to alternative antidepressant therapies, such as ketamine and electroconvulsive therapy (Lucido *et al.* 2021). Moreover, at least two studies have demonstrated that increased inflammation (as reflected by a CRP level > 1 mg/L) predicts a poor response to the serotonin reuptake inhibitor escitalopram and a much better response to drugs that affect dopamine, such as bupropion and nortriptyline, the latter of which has been shown to increase dopamine in the prefrontal cortex (Lucido *et al.* 2021). The better response to dopaminergic drugs predicted by biomarkers of increased inflammation is consistent with the effects of inflammation on dopamine in reward pathways. These findings suggest that measuring inflammatory biomarkers such as CRP prior to treatment might help guide antidepressant choice, with a preference for dopaminergic therapies in patients with high inflammation as opposed to serotonin reuptake inhibitors (Lucido *et al.* 2021).

Finally, it should be noted that there is a literature on the effects of antidepressant and antipsychotic medications on immune responses, including inflammation. Although antiinflammatory effects have been observed with both classes of medications in vitro and in vivo, the literature is somewhat mixed, and it remains unclear whether this immune activity is related to the clinical efficacy of these medications.

Given what we know about brain-immune system interactions, there are many opportunities to optimize future clinical trials to ensure that any effects of antiinflammatory strategies, if they exist, will be revealed (Miller and Raison 2015, 2016). To date, few studies have stratified patients by level of inflammation, and few studies have examined target engagement by the antiinflammatory drug, such as by inhibiting inflammation and then correlating the inhibition with treatment response. Importantly, no study has used what we know about the neurotransmitters and neurocircuits affected by inflammation to adjust outcome variables to reflect the most common inflammation-related symptoms, including anhedonia. Indeed, all three studies that used anticytokine therapies to treat patients with depression found a consistent effect on anhedonia (Lee *et al.* 2020; Raison *et al.* 2013b; Salvadore *et al.* 2018). Taken together, these shortcomings have prompted a series of recommendations to guide future clinical trials. First, clinical trials should either stratify patients into high-and low-inflammation groups (with the hypothesis that only the high-inflammation group should respond to an antiinflammatory intervention) or only include patients with increased inflammation. Second, a measure of target engagement should be provided, notably a biomarker of inflammation either in the brain or at the periphery, that demonstrates that inflammation indeed has been inhibited in those with increased inflammatory markers at baseline. Biomarkers in this regard may also include neurotransmitter systems or neurocircuits that are known to be affected by inflammation. Changes in biomarkers should in turn be correlated with changes in relevant symptoms. Third, primary outcome variables should include objective and clinical measures of symptoms that are known to be associated with inflammation and its effects on the brain, notably anhedonia. Given that studies to date have not taken advantage of the opportunities provided by a specific pathophysiological pathway that is being targeted in psychiatric patients, most of the data we have hails from traditionally designed clinical trials in which heterogeneous groups of patients are administered a drug with the hope that there will be some nonspecific overall response. The role of inflammation in neuropsychiatric disease provides a new path that eschews outdated trial designs and moves toward more precision-based studies derived from our understanding of the specific pathophysiology involved.

Conclusion

It is important to appreciate that mental and physical health are maintained through multidirectional interactions among psychological factors and the nervous, endocrine, and immune systems and other physiological systems of the body. Thus, it should come as no surprise that dysregulated multisystem interactions are often involved in mediating the underlying pathology of numerous diseases. In this chapter we have reviewed a few important examples of ways in which the nervous and endocrine systems affect immune function and the ways in which the immune system in turn affects the nervous system and behavior in the context of health and disease. Much work remains to be done to further elucidate mechanisms and translate findings from bench to bedside. However, elucidation of brain-immune system pathways and mechanisms is likely to be critically useful for restoring health in the presence of disease or promoting health in the absence of disease.

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CHAPTER 6

Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics

Joseph F. Goldberg, M.D.

This chapter addresses core concepts about the mechanics of how the body processes psychotropic medications, with a focus on pragmatic clinical applications. As the modern pharmacopoeia continues to expand, clinicians find themselves with an ever-increasing range of medication options to treat psychiatric disorders in all their diversity--from complex and treatment-resistant to comorbid presentations across varied dimensions of psychopathology. Never has it been more critical for practitioners to recognize the mechanistic rationales behind psychotropic drugs, or their safe and reasonable use either alone or in deliberate combinations intended to target specific symptom constellations. Given the increasing interest and emerging database on the possible genetic determinants of drug treatment outcomes, this chapter will also highlight current information about the evidence base for or against pharmacogenomic testing, focusing on its strengths and limitations as a clinical tool for practicing psychopharmacologists.

Basic Definitions

Pharmacokinetics refers to the effects of the body on a drug; *pharmacodynamics* refers to the effects of a drug on the body. *Bioavailability* refers to the proportion of an administered drug that enters the circulatory system and is available for uptake by site-of-action organs; it can be operationally defined by comparing the ratio of the areas under the curve (AUCs) for blood concentration versus time for the extravascular versus intravascular formulations of a given compound. Drugs that are intravenously administered are, by definition, 100% bioavailable. Drugs that are administered by all other routes generally have diminished bioavailability by virtue of *first-pass effects*. (Indeed, drugs that undergo extensive first-pass metabolism, such as ramelteon, have

extremely low oral bioavailability.) First-pass metabolism occurs predominantly in the liver but also in the intestinal epithelium (e.g., by localized catabolic enzymes such as cytochrome P450 [CYP] 3A4) and, to some degree, the lungs and circulatory system/vascular endothelium. Intranasal, inhaled, sublingual, intramuscular, and transdermal drug administration routes often yield higher bioavailability than oral administration because first-pass hepatic metabolism is at least partly avoided.

Note also the concept of *bioequivalence*, which involves establishing comparable bioavailability across different drug formulations--that is, demonstrating a similar rate and extent of drug availability at the intended site of action. Bioequivalence is particularly relevant when one is comparing generic versus branded drug formulations, or one branded version with another. The World Health Organization, as well as the FDA, consider two agents to have bioequivalence if the 90% confidence interval of their relative plasma level AUCs and C_{max} distributions (as defined below) fall within 80%-125% of each other. This rather wide range means that it is possible for some drugs with more variable bioavailability to show more heterogeneous effects (yet still fall within acceptable standards) when a switch is being made from a branded to a generic formulation. Therefore, drug efficacy and possible adverse effects can differ between a generic and a branded drug formulation, as has been shown in the case of carbamazepine and levothyroxine, as well as for some manufacturers' generic formulations of bupropion XL 300 mg.

Pharmacokinetics entails four main physiological functions--absorption, distribution, metabolism, and elimination.

Absorption

Absorption refers to the process by which a metabolically active foreign compound (a xenobiotic) is introduced into the body (orally, parenterally, intramuscularly, intrathecally, transdermally, topically, sublingually, or by inhalation) and is available to enter the circulatory system for transport to an intended site of action. Absorption may be *zero-order* (constant, as occurs during an intravenous ketamine infusion for major depressive disorder [MDD]) or *first-order* (where the rate of absorption follows a linear trajectory that is proportional to the amount of drug not yet absorbed, as occurs with most oral medications). Once orally administered drugs become solubilized in the gastrointestinal tract, they can enter the systemic circulation by one of four mechanisms: 1) passive diffusion (occurring for low-molecular-weight drugs driven by a high-to-low concentration gradient across a membrane); 2) facilitated (carrier-mediated) passive diffusion (involving transport from *low* to *high* concentration gradients [e.g., glucose]); P-glycoprotein is an example of a transporter protein that extrudes toxins back into the gut intestinal lumen, as well as across the blood-brain barrier; 3) active transport; or 4) pinocytosis. Passive diffusion depends on a parameter known as the *lipid-water partition coefficient* (K_p), defined as the ratio of drug in the lipid phase versus the aqueous phase, with high K_p values reflecting high drug solubility. Factors that influence absorption include the route of administration, drug solubility, and rate of gastric emptying. Certain parameters are worth noting regarding the absorption of specific psychotropic agents. Gabapentin, for example, is absorbed from the intestines by an active transport mechanism that becomes saturated at doses greater than 1,200 mg at any one time. A proprietary once-daily gastroretentive formulation (Gralise) permits absorption of higher doses, while gabapentin enacarbil has about twice the oral bioavailability of immediate-release gabapentin and is absorbed through a different, less-saturable transport mechanism.

Distribution

Distribution refers to the process by which a drug is transferred from the systemic circulation to site-of-action organs. Some psychotropic drugs are transported from their site of absorption to their site of action via carrier proteins in the circulatory system (mainly albumin, but potentially also globulins or lipoproteins). Notable examples include diazepam or divalproex. Ultimately, unbound or free fractions of a drug are able to diffuse through capillary walls. In patients with low serum albumin levels (e.g., due to hepatic dysfunction, malnutrition, or increased albumin degradation due to renal impairment), it can be useful to measure the unbound fraction of a drug that is ordinarily highly protein bound in order to obtain a physiologically more accurate estimate of bioavailable drug, as illustrated in Clinical Vignette 1 below. Highly protein-bound drugs tend to have low metabolic clearance.

Clinical Vignette 1

A 154-pound 26-year-old man hospitalized for bipolar mania was orally loaded with divalproex extended release (divalproex ER) at 25 mg/kg once daily, yielding a projected therapeutic dosage of 1,750 mg/day, intended to produce a trough plasma valproate level between 85 and 125 mg/mL. A Day 5 trough valproate level was subtherapeutic at 31 mg/mL. A comprehensive metabolic profile revealed a low serum albumin level of 2.2 g/dL (laboratory reference range: 3.4-5.4 g/dL). A free serum valproic acid level was ordered and found to be in the high end (18 mg/mL) of the laboratory reference range (6-22 mg/mL). There were no clinical signs of gastrointestinal or neurological toxicity (e.g., nausea/vomiting or tremor and ataxia, respectively) and, accordingly, dosing was not changed. Workup of hypoalbuminemia revealed no evidence of renal disease/proteinuria, chronic medical disease, hepatic dysfunction, burns, or obvious malnutrition. However, anti-tissue transglutaminase IgA antibody testing was positive, consistent with a diagnosis of celiac disease, accounting for likely malabsorption as the cause of his hypoalbuminemia. The patient was referred for further gastrointestinal workup as his psychiatric symptoms improved with no further change to his regimen.

Metabolism

Drugs that undergo metabolism do so either through enzymatic degradation in the liver through phase I (consisting of CYP isoenzymes), which involves mainly oxidation, or phase II hepatic metabolism (described further in the section "Phases of Drug Metabolism"). Some CYP metabolic reactions also occur outside the liver; for example, CYP3A and CYP2C are found not only in the liver but also in the intestinal mucosa (Thelen and Dressman 2009). Gut CYP3A4 is rapidly and irreversibly inhibited by dietary CYP3A4 inhibitors such as grapefruit juice. Some drugs also undergo no metabolism and are simply eliminated unchanged in urine and/or feces (e.g., lithium, gabapentin).

Elimination

Drugs are eliminated from the body mainly either via renal excretion or by excretion into the bile (usually without undergoing hepatic metabolism), with subsequent passages into feces. Trace amounts of drugs are also eliminated through sweat, breast milk, saliva, or exhaled air. Renal excretion is the dominant mode of elimination for most psychotropic drugs and depends on intact kidney function. Renal function is traditionally measured by the glomerular filtration rate (GFR), which in turn is estimated (eGFR) from the patient's creatinine clearance (CrCl).

eGFR was formerly estimated using the Cockroft-Gault equation, which has fallen into disfavor for clinical (nonresearch) purposes because a) it does not take into account body surface area, and b) it has not been expressed using standardized creatinine values. The Cockroft-Gault equation has largely been replaced by either the Modification of Diet in Renal Disease (MDRD) equation (Levey *et al.* 1999) or the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (Levey *et al.* 2009):

MDRD $$\text{eGFR} = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}),$$

where S_{cr} is serum creatinine in mg/dL and Age is in years.

CKD-EPI $$\text{eGFR} = 141 \times \min(S_{cr}/k, 1)^{a} \times \max(S_{cr}/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times (1.018 \text{ if female}) \times (1.159 \text{ if African American}),$$

where S_{cr} is serum creatinine in mg/dL, k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/k or 1, max indicates the maximum of S_{cr}/k or 1, and Age is in years.

A normal eGFR is approximately 97-137 mL/min in men and 88-128 mL/min in women. GFR declines by about 10 mL/min for every decade after age 40 and also depends on weight. Some authors have noted that serum creatinine may be a less sensitive measure for milder degrees of renal insufficiency, or may be less accurate because of artificially elevated serum creatinine levels in certain populations (e.g., body builders who regularly lift weights or consume creatine ethyl ester supplements); cooked meats also convert skeletal muscle creatine to creatinine, and ingestion within 12 hours of measuring serum or urine creatinine levels has been shown to significantly increase measurable amounts (Nair *et al.* 2014). Serum cystatin C, a low-molecular-weight renally filtered protein, is sometimes measured as an alternative to serum creatinine in estimating (or corroborating) true GFR (Shlipak *et al.* 2013).

A drug's elimination is closely linked with its metabolism. Useful parameters for understanding drug exposure and elimination include the following:

Area under the curve (AUC): a graphical plotting of the plasma concentration of a drug (along the y-axis) by time (along the x-axis).

C_{max}: the maximal concentration of a drug, reflecting both the rate and the extent of absorption of that drug. C_{max} is highly correlated with AUC. Some authors suggest that the ratio of C_{max} to AUC is more useful than C_{max} alone for estimating bioequivalence of absorption rates across compounds (Endrenyi *et al.* 1991).

C_{min}: the minimal blood concentration of a drug, or trough level, as measured just before a next dose occurs.

For some orally administered drugs, C_{max} and AUC can both be affected by the presence or absence of food, as noted for specific compounds listed in the pharmacokinetic tables included at the end of this chapter.

Kinetics of Drug Elimination

Biological half-life refers to the time necessary for a drug either to a) reach half of its steady-state serum concentration (C_{ss}) or b) become reduced by half of its C_{ss} (termed *elimination half-life*). As a rule of thumb, the passage of five half-lives is necessary in order for a drug either to achieve C_{ss} once it has been introduced or to become fully eliminated from the circulatory system. There are a number of caveats attached to the concept of the passage of five half-lives. First, some drugs can exert meaningful biological activity without the need to reach C_{ss}. For example, in the case of some second-generation antipsychotics with long half-lives and/or availability in the form of long-acting injectables, such as aripiprazole or risperidone, achievement of a clinically meaningful serum level (i.e., the threshold of 150-300 ng/mL [Kirschbaum *et al.* 2008]) occurs within several days after administration (even though C_{ss} may take at least 2 weeks to achieve). Second, the concept of half-lives is more directly relevant to drugs that bind to receptor targets than to drugs that exert pharmacodynamic effects by inhibiting enzymes. For example, traditional monoamine oxidase inhibitors (MAOIs) irreversibly inhibit monoamine oxidase, which in turn cannot regenerate for at least 2 weeks--even though the half-life of drugs such as tranylcypromine or isocarboxazid is relatively short (see appendix to this chapter). Drugs or compounds that inhibit CYP enzymes rapidly and irreversibly shut down the enzyme (e.g., grapefruit juice and CYP3A4), which then may take from 1 to 3 days to regenerate. Third, half-lives refer to steady-state pharmacokinetics in the bloodstream but may not necessarily be particularly informative about the bioavailability of a drug at its end-organ site(s) of action. For example, lithium (as a lipophilic ionophore) can remain in brain and bone tissue long after serum levels become zero (as often occurs following a toxic overdose). The selective serotonin reuptake inhibitor (SSRI) fluvoxamine also has been shown by magnetic resonance spectroscopy to have a brain elimination half-life of 58 hours but a plasma elimination half-life of about half that (26 hours) (Strauss *et al.* 1998).

Drugs with a relatively short half-life do not necessarily require multiple daily doses. For example, risperidone has a fairly short half-life of about 3 hours, but its active metabolite 9-hydroxy-risperidone (i.e., paliperidone) has a half-life of about 30 hours. Nefazodone follows nonlinear (first-order) pharmacokinetics (defined in the next section); its pharmacokinetics (C_{min} and AUC) appear similar with once-or twice-daily dosing (Marathe *et al.* 1996). Quetiapine, despite a terminal elimination half-life of around 6 hours, has been studied and used successfully with once-daily (nighttime) dosing for bipolar depression to minimize daytime sedation (e.g., Calabrese *et al.* 2005).

The concept of drug "clearance" is really an amalgam of the processes of metabolism and elimination. The clearance rate of a drug follows different mechanics depending on the extent to which saturation or nonsaturation of a (catabolic) enzyme affects the breakdown of its substrate. Three kinds of elimination kinetics have been described.

Zero-order elimination kinetics means that metabolism *becomes saturable* in excess and a *constant amount* of drug is eliminated per unit time, regardless of the plasma concentration. In other words, the rate of reaction depends solely on time and not drug concentration, as depicted in Figure 6-1A, and plasma concentration declines proportionally with time as shown in Figure 6-1B. Few drugs follow zero-order kinetics. Pertinent examples include ethanol, methanol, fluoxetine, and phenytoin. Such drugs will build up higher concentrations over time as compared to those that follow first-order kinetics.

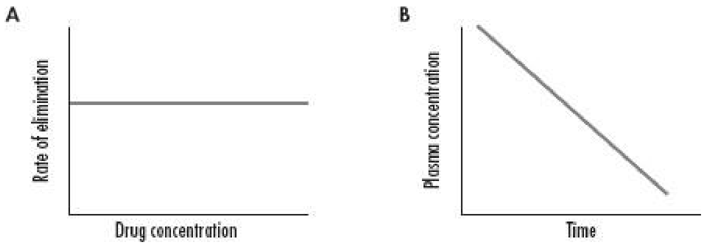

FIGURE 6-1. Zero-order elimination kinetics.

(A) Rate of reaction depends solely on time and not drug concentration. **(B)** Plasma concentration declines proportionally with time.

The majority of psychiatric drugs are eliminated by *first-order kinetics*. In first-order kinetics, a *constant proportion* of drug is eliminated per unit time, and the process is entirely dependent on drug concentration (i.e., drugs at higher concentration are eliminated faster than drugs at lower concentration) and driven mainly by diffusion. Drug elimination in first-order kinetics follows an exponential decay curve, as shown in Figure 6-2A. Plotted on a logarithmic scale, the relationship between drug concentration and elimination rate is depicted in Figure 6-2B. Elimination increases proportionally as drug concentration increases. First-order elimination kinetics is thus considered a linear process because the rate of elimination is proportional to the drug concentration (i.e., the elimination process cannot become saturated).

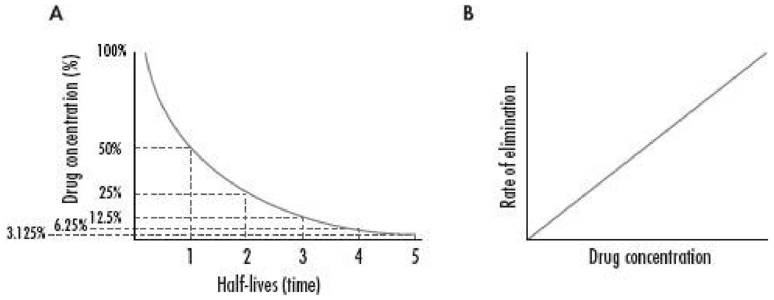

FIGURE 6-2. First-order elimination kinetics.

(A) Exponential decay across five elimination half-lives of a drug that follows first-order elimination kinetics. **(B)** First-order elimination kinetics plotted as a logarithmic function.

Nonlinear kinetics occurs if the availability of a metabolic enzyme becomes saturated, such that further increases in drug concentration no longer cause increased elimination (as is the case in first-order kinetics). Thus, *second-order elimination* involves a logarithmic growth curve when plotting the rate of enzymatic reaction (y-axis) by drug dose, as depicted in Figure 6-3A. When elimination is expressed as the relationship between steady-state drug concentrations (y-axis) and further dose increases (x-axis) (Figure 6-3B), we can see that in the setting of high drug concentrations, even minor drug dosage changes will cause substantial further increases in drug concentration. The graph shown in Figure 6-3A depicting logarithmic second-order elimination kinetics also reflects the saturation curve described by the Michaelis-Menten equation, explaining how the rate of an enzymatic reaction increases as the substrate concentration increases:

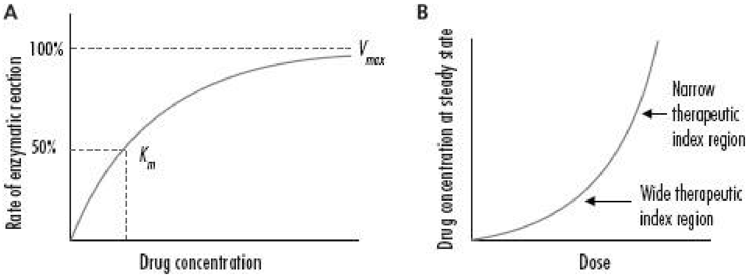

FIGURE 6-3. Second-order elimination kinetics.

(A) Logarithmic growth curve obtained by plotting the rate of enzymatic reaction (y-axis) by the drug concentration (x-axis). **(B)** Second-order elimination expressed as the relationship between steady-state drug concentrations (y-axis) and further dosage increases (x-axis). K_m = drug concentration at 50% of V_{max}; V_{max} = maximal rate of reaction.

$$V = \frac{V_{max} \times [S]}{K_m + [S]},$$

where V equals the velocity or rate of a reaction, V_{max} represents the maximum rate of the reaction, $[S]$ represents the substrate (drug) concentration, and K_m indicates the substrate concentration at 50% of V_{max}.

A further practical implication of drugs that follow second-order elimination kinetics involves therapeutic indices. Medications with concentration ranges toward the less steep left-hand side of the curve in Figure 6-3B tend to have broader therapeutic indices (i.e., small changes in dosage will not so drastically affect serum levels),

whereas concentrations toward the steeper right-hand side of the curve have narrower therapeutic indices. Correspondingly, incremental dosage increases may be more likely to lead to toxicity states. Drugs that must achieve 50% of V_{max} (i.e., K_m) to exert a meaningful pharmacodynamic effect are often considered to have a narrow therapeutic index. Psychotropically relevant examples of drugs with narrow therapeutic indices are lithium carbonate, carbamazepine, and levothyroxine.

Dose-Response Relationships

Dose-response curves are graphical depictions of the relationship of the magnitude of biological activity or pharmacodynamic effect of a drug (plotted on the y-axis) relative to increasing doses. When plotted as a logarithmic function, drug dose-response curves are often sigmoidal, as depicted in Figure 6-4.

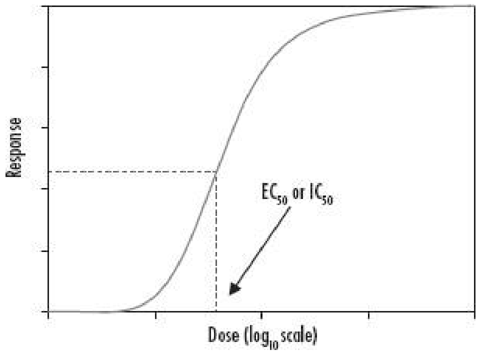

FIGURE 6-4. Sigmoidal drug dose-response curve.

EC_{50} = half-maximal effective concentration; IC_{50} = half-maximal inhibitory concentration.

The *half-maximal effective concentration* (EC_{50}) of a drug is sometimes taken as an indicator of potency, referring to the plasma concentration of a drug needed to obtain 50% of a maximal pharmacodynamic effect. EC_{50} is defined by the inflection point in the sigmoidal curve shown in Figure 6-4. Analogously, the *half-maximal inhibitory concentration* (IC_{50}) refers to the dose or concentration of a drug needed to inhibit half of the maximal response to an agonist.

Extended-Release Drug Formulations

Extended-release formulations of compounds do not necessarily alter the elimination half-life of a drug but may alter bioavailability because of differences in the delivery system between formulations. For example, divalproex ER produces about an 8%-20% lower serum valproic acid level than occurs with the conventional (delayed-release) formulation of divalproex (Sommerville *et al.* 2003)--meaning that the extended-release formulation is often dosed 20% higher than the delayed-release formulation to achieve bioequivalence. The extended-release formulation of quetiapine (quetiapine XR) has the same half-life as immediate-release (IR) quetiapine (about 6 hours), but the IR formulation has a considerably higher C_{max} and faster time to peak plasma concentration (T_{max}), which could have implications for the time course and magnitude of adverse effects such as sedation.

Extended-release compounds may have the pharmacokinetic advantage of minimizing excursions from maximal to minimal blood levels (C_{max} and C_{min}, respectively), and it is often at least theoretically possible that nighttime dosing can sometimes minimize the impact of possible adverse effects (such as sedation with antihistaminergic drugs) when C_{max} occurs during sleep. Notably, extended-release formulations of a drug generally do not alter a drug's terminal elimination half-life; rather, they involve enteric coatings, osmotic pumps, or other release systems that slow the release of a drug from the gastrointestinal to the circulatory system. Maximal peak and trough concentrations of an extended-release drug are thereby achieved based more on absorption than on elimination.

Extended-release formulations tend to be absorbed more distally in the gastrointestinal tract and consequently provide less reliable forms of drug delivery in patients who have undergone bariatric surgery, including restrictive procedures (i.e., gastric sleeve or banding) or both restrictive and malabsorptive procedures (i.e., gastric bypass, or Roux-en-Y procedure). Bariatric surgery can impair gastric motility, decrease gastric volume, raise gastric pH (potentially decreasing the solubility of basic drugs and increasing the solubility of acidic drugs), and decrease surface area for gastric absorption. After gastric bypass, first-pass metabolism of CYP3A4 substrates may decrease, and less contact with biliary secretions and carrier proteins (e.g., P-glycoprotein) can alter absorption and elimination, potentially necessitating lower drug dosages to achieve desired effects.

Orally disintegrating forms of a drug generally have the same half-life and bioavailability as non-orally disintegrating formulations. Drugs with long terminal elimination half-lives (i.e., > 24 hours) generally can be dosed once daily with little concern about reliable pharmacodynamic efficacy; however, tolerability may sometimes require oral administration in divided doses to minimize adverse effects (e.g., gastrointestinal or neurological adverse effects from high-dose lithium or divalproex--either of which can in principle be taken once daily).

Examples of key pharmacokinetic parameters for commonly used psychotropic drugs are summarized in the tables presented in the appendix to this chapter.

Phases of Drug Metabolism

Hepatic drug metabolism is divided into two phases. *Phase I* involves conversion of a drug to more polar (water-soluble) molecules via oxidation (e.g., hydroxylation, dealkylation, deamination), reduction, and hydrolysis reactions, mediated primarily by CYP isoenzymes. *Phase II* metabolism involves conjugation of drug or phase I metabolites with other molecules, as occurs during glucuronidation (e.g., via uridine diphosphate [UDP]-glucuronosyltransferase), acetylation (e.g., via *N*-acetyltransferase), methylation (e.g., via methyltransferase), sulfonation (e.g., via sulfotransferase), glutathione conjugation (e.g., via glutathione-*S*-transferase), and amino acid conjugation (e.g., via aminoacyl-transfer RNA [tRNA] synthetases). "Slow acetylator" genotypes (seen among 40%-70% of white and Black individuals, 10%-20% of Japanese and Canadian Eskimos, and 80% of Egyptians) lead to inefficient acetylation of drug substrates for *N*-acetyltransferase, potentially causing higher-than-usual blood levels and adverse effects; among psychotropic compounds, phenelzine is perhaps the most commonly observed drug that is appreciably metabolized by acetylation.

As discussed in a later section of this chapter, genetic variants in CYP enzymes, and at least some phase II enzymes, can influence the rate and extent of catabolism for their substrate drugs and are a foundation for understanding the pharmacogenetic influence on pharmacokinetics.

Therapeutic Drug Monitoring: When Is It Useful?

Measurement of serum drug levels for a parent compound (say, fluoxetine or clozapine) and sometimes its active metabolite(s) (say, norfluoxetine or norclozapine, respectively) varies in its practical usefulness. Some compounds have well-established therapeutic reference ranges that inform prescribers about optimal dosing (e.g., nortriptyline, for which therapeutic response based on blood levels follows a bell-shaped curve) and the likelihood of "diminishing returns" (i.e., more adverse effects without more efficacy) with dosing beyond an upper threshold. Other agents might have narrow therapeutic indices (see Figure 6-3B), meaning that a laboratory reference range for blood levels not only corresponds to efficacy or "diminishing returns" but in fact encroaches on more hazardous toxicity beyond an upper limit (lithium represents probably the best example here). Elsewhere, there are compounds for which "therapeutic" reference ranges have been established for pharmacodynamic efficacy unrelated to psychotropic properties--notably, in the case of anticonvulsants such as carbamazepine or lamotrigine, where serum levels are more informative about likelihood of adequate seizure prophylaxis, but not necessarily mood-stabilizing properties. Or, a drug may have an established therapeutic reference range for blood levels that pertains only to a particular phase of illness (as in the case of serum valproic acid levels for acute mania, but not for acute bipolar depression or for relapse prevention). In empirical studies, plasma levels for certain compounds, such as fluoxetine and its active metabolite, norfluoxetine, have been shown *not* to correlate with relapse after initial response (Brunswick *et al.* 2002), perhaps in part because fluoxetine displays zero-order rather than first-order kinetics.

Therapeutic drug monitoring can be useful in the following contexts:

Tracking adherence. It is simple enough to measure a serum level of almost any drug merely for the sake of affirming that the compound is present in the body. Such "affirmation" may vary considerably based on the half-life of a given drug, meaning that haphazard adherence to a regimen will be detected with less sensitivity in a compound with a long half-life (e.g., aripiprazole or cariprazine) than in a compound with a short one (e.g., ziprasidone).

Monitoring for toxicity. Particularly in the case of drugs with narrow therapeutic indices, laboratory plasma reference ranges can affirm when observed adverse effects may indicate toxicity (e.g., tremor with lithium or divalproex; ataxia with carbamazepine).

Monitoring for pharmacodynamic efficacy. Therapeutic reference ranges for plasma drug concentrations have been established and validated for some, but not all, psychotropic compounds. Examples include most tricyclic antidepressants, lithium during the acute and maintenance phases of treatment for bipolar disorder, clozapine in schizophrenia, and divalproex for acute bipolar mania. A more provisional literature supports the use of tracking serum levels of O-desmethylvenlafaxine for predicting response to venlafaxine (e.g., Stamm *et al.* 2014) or duloxetine serum levels for predicting duloxetine antidepressant response (e.g., De Donatis *et al.* 2019). Among antipsychotics, serum clozapine levels above 350 ng/mL have been associated with more robust efficacy in schizophrenia (VanderZwaag *et al.* 1996), with more provisional and preliminary findings reported with a handful of other second-generation antipsychotics (notably, olanzapine, risperidone, and aripiprazole [reviewed in Goldberg and Stahl 2021]). High interindividual variability in serum drug concentrations relative to dosing has posed a limitation for drawing generalizable inferences about drug levels and pharmacodynamic response for many compounds.

Gauging room for improvement. Available therapeutic plasma concentration ranges can help to guide or inform optimal dosing because they provide general estimates about the likelihood of achieving and sustaining a therapeutic effect based on population studies. As such, however, they may not necessarily translate to every individual; a clinically stable patient with a technically subtherapeutic nortriptyline or lithium blood level may not necessarily benefit from higher dosing simply to achieve a higher plasma level in the absence of symptoms (they might, however, incur more adverse effects). At the same time, measuring a serum drug level in a patient who remains clinically symptomatic can help establish room for upward dosing with expected tolerability.

Monitoring pharmacokinetics in special situations. In the clinical settings of malnutrition, hypoalbuminemia, and malabsorption syndromes, measuring the free/unbound fraction of protein-bound drugs (e.g., valproate) may yield information about possible impaired absorption or distribution, as noted above in Clinical Vignette 1. In pregnancy, lamotrigine levels may decline substantially throughout all trimesters as a result of estradiol upregulation of *UGT1A4* gene expression and increased clearance of lamotrigine by as much as 175%--thus constituting one of the rare instances in which serum lamotrigine levels are viewed by some authors as having clinical relevance in psychiatry (Clark *et al.* 2013). See Clinical Vignette 2 below for a more detailed illustration of lamotrigine dosing management during pregnancy.

Assessing pharmacokinetic interactions. Monitoring of serum drug levels can be useful (and often necessary for safety purposes) when drugs that inhibit or induce metabolic enzymes are being coprescribed. Examples would include following tricyclic antidepressant levels when coprescribing SSRIs that inhibit CYP2D6.

Clinical Vignette 2

A 28-year-old woman with bipolar disorder, most recent episode depressed and in remission, was stably maintained for over 1 year on lamotrigine 200 mg/day with quetiapine 300 mg/day. Her stated plan to become pregnant prompted a clinical review affirming the benefits and relative safety of her current regimen during pregnancy. A decision was made to measure a baseline (reference) serum lamotrigine level preconception, which was 4.2 mg/mL (laboratory reference range: 2.5-15 mg/mL). She conceived within 6 months. Some authors advocate measuring serum lamotrigine levels every 4 weeks during pregnancy, with automatic dosage increases by 20%-25% if a monthly serum level falls below the reference concentration (Sabers 2012), although others question the necessity of this as a routine practice because reductions in serum lamotrigine levels do not necessarily translate to increased symptoms (Sharma and Sommerdyk 2014). The patient was followed clinically by her psychiatrist on a monthly basis and weekly by her nonmedical psychotherapist. Around week 26 of her pregnancy she reported increased low-grade depressive symptoms, and a serum lamotrigine level measured at that time was 1.3 mg/mL. Dosing was increased to 250 mg/day, with improvement in depressive symptoms throughout the remainder of the pregnancy. A serum lamotrigine level measured 3 weeks postpartum was 5.1 mg/mL. Although that level was 21% higher than her reference concentration, the modestly higher dose was continued because it was well tolerated and she was euthymic.

When should serum drug levels be measured? Random levels may inform about the sheer presence or absence of a drug in the bloodstream but tell us little about therapeutic ranges or optimal dosing and consequently should not form the basis for decisions about optimized dosing. True trough serum levels of any drug are those measured *just before a next dose occurs* (regardless of the half-life of the molecule) (i.e., corresponding to C_{min}). In patients taking divalproex ER, serum valproate levels are ideally measured *no sooner* than 18 hours after the last dose in order to provide an estimate that is within 13% of the true trough value (Reed and Dutta 2006). The International Society of Bipolar Disorders/International Study Group on Lithium advises measuring a serum lithium level 12 +- 1 hours after a last ingestion in patients for whom lithium is dosed either once or twice daily (Nolen *et al.* 2019). Measurement of the 12-hour serum lithium level in patients who are using once-daily dosing may overestimate the true trough level, prompting some authors to advise multiplying the 12-hour level by 1.3 to better reflect the likely true trough and avoid underdosing (Reddy and Reddy 2014). Meaningful serum levels in general also are most interpretable when obtained no sooner than the passage of five elimination half-lives, in order to gauge steady-state kinetics.

Estrogens and progestins are metabolized by CYP3A4 and, as such, are subject to enzyme induction by several anticonvulsant drugs that induce 3A4. Table 6-1 summarizes clinically relevant known interactions between estrogen (either when formulated in oral contraceptives, as hormone replacement therapy, or during pregnancy) and anticonvulsants with known psychotropic effects.

TABLE 6-1. Pharmacokinetic effects of anticonvulsants on estrogen

Agent	Pharmacokinetic effect
Carbamazepine	Carbamazepine significantly reduces levels of estradiol.
Divalproex	Divalproex may reduce efficacy of estrogen-containing oral contraceptives.
Gabapentin	None
Lamotrigine	Estrogen (17-b-estradiol) upregulates uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A4 2.3-fold, thereby increasing the metabolism of lamotrigine by about 50%; lamotrigine does not affect oral contraceptive levels.
Oxcarbazepine	Oxcarbazepine can decrease plasma concentrations of ethinylestradiol or levonorgestrel, potentially reducing contraceptive effectiveness.
Pregabalin	None
Topiramate	Topiramate increases estrogen metabolism.

Let us now turn more explicitly to a discussion of pharmacodynamics, beginning with the basis for drug efficacy (and tolerability) according to our understanding of drug/receptor target interactions.

Pharmacological Rationales: Do Drug Mechanisms of Action Matter?

Our knowledge of drug mechanisms of action remains rudimentary and largely inferential from preclinical studies examining suspected neurocircuits that underlie manifestations of psychopathology. While the field has long since moved past oversimplified explanations about monoaminergic "chemical imbalances" to explain mood disorders, or simplistic theories that schizophrenia results from "too much" or "too little" dopamine in the brain, the precision with which we can craft better drug interventions for serious mental disorders--or personalize treatments based on neurobiological parameters of any one individual patient--remains elusive. The field has come to think of dysregulated circuits, or neural networks, rather than neurotransmitters themselves, as more central to understanding psychopathology. Intended treatment targets focus more on downregulating or upregulating (or "tweaking" or fine-tuning) circuitry.

Receptor Binding Affinities and Ligand Dissociation

Drugs typically exert their pharmacodynamic effects by interacting either with receptors (such as inhibiting a transporter) or a catabolic enzyme (e.g., monoamine oxidase) to prevent neurotransmitter degradation. Ligand-receptor interactions are categorized based on agonist, antagonist, or partial agonist effects. Ligands engage their receptor targets with binding affinities that are measured as dissociation constants (K_d's)--a type of equilibrium constant--expressed in nanomoles (nM). Note that the terms K_i and K_d both represent measures of binding affinity between a ligand and a receptor. K_d denotes the dissociation constant for any ligand-receptor complex, whereas K_i refers more specifically to an enzyme-inhibitor complex. In general, drugs with low K_d's (i.e., low dissociation, meaning high affinity) exert potent pharmacodynamic effects at a given receptor, with consequent reflection in their perceived mechanism of action. Drugs with high binding affinities at specific receptors are often viewed as potent candidates for pharmacodynamic effects associated with that receptor, whether desired or undesired. For example, potent antagonism at a_1 receptors is thought to drive orthostatic hypotension (as seen with trazodone, prazosin, and second-generation antipsychotics such as risperidone or quetiapine).

Ligands with low K_d's are considered "tight" binders, whereas those with higher K_d's bind more loosely. Thus, antipsychotics with low K_d's at the D_2 receptor may predispose to a higher likelihood of adverse extrapyramidal effects, including acute dystonic reactions. In the early 2000s, Kapur and Seeman (2001) proposed the hypothesis that the pharmacodynamic "atypicality" of second-generation antipsychotics came from rapid dissociation from their D_2 receptor binding targets (eventually known as the "fast onset/fast offset" hypothesis). In this model, "loose" D_2 binding from agents with high K_d's presents an attractive strategy to minimize adverse dopalytic effects in the dorsal striatum and tuberoinfundibular pathways while preserving intact efficacy in mesocortical and mesolimbic tracts. Later authors have suggested that drug accumulation in the lipophilic cell interior might underestimate the speed of dissociation from D_2 receptors (Sahlholm *et al.* 2016).

Antihistaminergic drugs such as cyproheptadine (K_d = 0.06 nM), hydroxyzine (K_d = 2.0-19 nM), quetiapine (K_d = 2.2-11 nM), and diphenhydramine (K_d = 9.6-16 nM) are thought to exert marked sedating effects by virtue of their tight binding affinities at the H_1 receptor.

The following terminology describes the nature of ligand-receptor interactions:

Agonist: An agonist is a ligand that binds to a receptor and produces an activating response similar to that produced by an endogenous compound (e.g., a neurotransmitter).

Antagonist: An antagonist is a ligand that binds to a receptor and prevents its activation. Antagonists can be either *competitive* (i.e., they bind at the same active site as an endogenous ligand) or *noncompetitive* (i.e., they either bind irreversibly to the active site, or they bind to an allosteric modulatory site on the receptor). Naloxone is an example of a competitive antagonist at the mu opioid receptor, which reverses the activity of an agonist (e.g., morphine).

Partial agonist: A partial agonist binds to a receptor at its active site (which is also called an *orthosteric site*) but produces only partial efficacy relative to a full agonist, with a response as depicted in Figure 6-5. An example is buprenorphine (a partial agonist at the mu opiate receptor and an antagonist at the kappa opiate receptor).

Inverse agonist: A drug that binds to the same receptor as an agonist but produces the opposite pharmacodynamic effect (tantamount to an antagonist). However, inverse agonists require that the receptor they bind to has *constitutive activity*. That means that the receptor maintains a basal level of activity even in the absence of ligand binding. Inverse agonists block the constitutive activity of agonists. Examples include flumazenil (which binds to the benzodiazepine site of the $GABA_A$ receptor) and the antipsychotic pimavanserin (which is an inverse agonist of the 5-hydroxytryptamine type 2A ($5\text{-}HT_{2A}$) receptor and is used in the treatment of Parkinson's disease psychosis). Naloxone, as noted above, is a competitive mu opioid receptor antagonist (used to prevent overdose from buprenorphine) but also can function as an inverse agonist.

Neutral antagonist: Also known as *silent antagonists*, neutral antagonists are ligands that bind to a receptor but exert no intrinsic activity or change in signaling response, although they can block the activity of a full or partial agonist or inverse agonist.

Allosteric modulators: Some ligand receptors have so-called allosteric modulatory sites, which are locations on a receptor that are physically different from the location where an endogenous ligand (e.g., a neurotransmitter) binds, and which lead to upregulation or downregulation of receptor activity. These sites contrast with *orthosteric* or *ion channel sites*, which are the primary unmodulated ligand binding site on a receptor. Allosteric modulatory sites are in themselves inactive but when bound change conformation in order to become pharmacologically active or inactive. Examples include the *N*-methyl-D-aspartate (NMDA) ionotropic glutamate receptor, which has *glycine* and *glutamate* regulatory (allosteric modulatory) binding sites, as depicted in Figure 6-6.

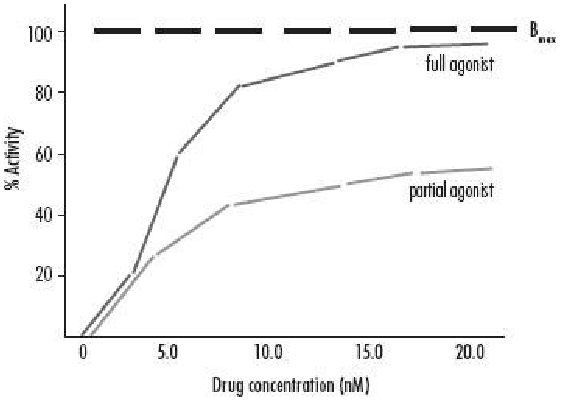

FIGURE 6-5. Dose-response curve for full and partial agonists.

B_{max} = maximal amount of bound drug; nM = nanomolar.

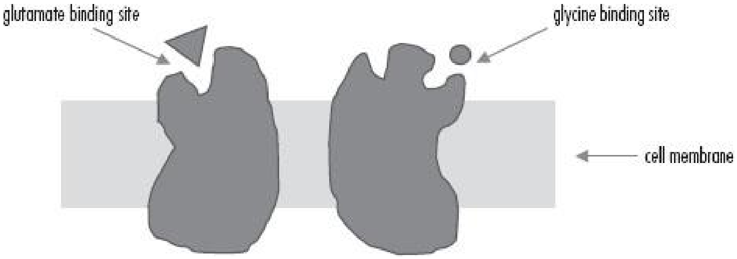

FIGURE 6-6. Allosteric binding sites on the *N*-methyl-D-aspartate (NMDA) receptor.

It was noted earlier in this chapter that we no longer think of psychopathology as resulting from "chemical imbalances" so much as dysregulation of neural circuitry, and modulation of neurotransmission along particular circuits or networks is thought to fine-tune signaling. We can now go one step further and speak of the specific receptor targets of neurotransmission in ways that might help to predict both drug efficacy and tolerability. Consider serotonergic circuitry as an example. An SSRI effectively increases the availability of serotonin quanta by blocking presynaptic reuptake. Imagine

a ship leaving its dock but then, upon return from its brief voyage, discovering that the dock (the serotonin transporter protein) is closed and that it must remain at sea longer than would otherwise be the case. Enhanced availability of serotonin quanta across the synapse could lead to indiscriminately enhanced postsynaptic binding, resulting in more "collateral damage" than one might hope for. "Indiscriminate" or undesired binding at some postsynaptic targets creates adverse effects; thus, agonism at the postsynaptic 5-HT_3 receptor causes nausea (perhaps the most common adverse effect across SSRIs); agonism at 5-HT_{2A} receptors can cause sexual dysfunction; agonism at 5-HT_7 receptors enhances GABA-mediated inhibition of serotonin release in the raphe nucleus; and antagonism at 5-HT_{2C} receptors can cause appetite increases and weight gain. A "smart" serotonergic drug would selectively agonize (activate) postsynaptic 5-HT_{1A} receptors (for a putative antidepressant and anxiolytic effect) while selectively blocking 5-HT_{2A}, 5-HT_3, and 5-HT_7 receptors and agonizing (activating) 5-HT_{2C} receptors.

Tachyphylaxis and Tolerance

True *tachyphylaxis* involves a rapidly diminishing pharmacodynamic response to repeated doses of a drug over a relatively short period of time. This response is a non-dose-dependent, rate-sensitive phenomenon that often resolves after a hiatus from drug administration. Common examples of drugs known to produce tachyphylaxis are psychedelics, opioids, and nicotine. (A frequent clinical dilemma involves differentiating tachyphylaxis from the progressive worsening of the natural course of an illness, for which a once-efficacious drug dosing regimen may simply become inadequate to overcome increasing severity of the underlying disease process.) *Tolerance*, by contrast, refers to the more gradual need for larger doses of a drug to achieve the same effect as previously established during long-term administration. It involves increased drug clearance and is believed to reflect downregulation of receptor number, function, or sensitivity. Chronic ethanol exposure would exemplify tolerance, in which CYP enzyme induction leads to accelerated clearance and the need for increasing doses to achieve a previously observed pharmacodynamic effect. The concept of *cross-tolerance* means than different drugs with similar receptor targets can be substituted for one another, as occurs when using benzodiazepines to detoxify patients from alcohol, or substituting one opiate for another (e.g., methadone for heroin) to avoid withdrawal.

In the case of tolerance that develops to MAOIs, serotonergic antidepressants, or psychostimulants, dosage increases often will at least temporarily overcome diminished efficacy (as limited by higher-dose potential safety considerations) and will be less disruptive than undertaking a drug holiday followed by rechallenge at usual starting doses. The absence of randomized trials examining tolerance to psychotropic drugs limits the evidence base from which to identify optimal management.

Drug Stereoisomers

Racemic versus enantiomeric formulations of psychotropic drugs can vary in their pharmacokinetics and pharmacodynamics. Levorotatory (left-handed) and dextrorotatory (right-handed) enantiomers of chiral molecules also can differ in drug potency. For example, dextroamphetamine has a shorter half-life and higher potency than levoamphetamine--making mixed amphetamine salts a less potent racemic formulation than the pure dextro molecule. Similarly, the *S*-enantiomer of ketamine is about three to four times more potent than racemic ketamine, but the intravenous mode of administration for racemic ketamine has higher bioavailability (by definition, 100%) than intranasal esketamine (about 50%). Enantiomeric armodafinil has a duration of effect that lasts about 2 hours longer than that of racemic modafinil. Levomilnacipran has a somewhat longer half-life (12 hours) and higher antidepressant potency than racemic milnacipran (8 hours). A pooled analysis comparing enantiomeric escitalopram versus racemic citalopram for MDD found a significantly greater reduction in depression severity scores and a higher response rate (56% vs. 41%) with the former than with the latter (Azorin *et al.* 2004).

Pharmacogenomics and Pharmacogenetics

The field of clinical therapeutics has increasingly moved toward the concepts of personalized medicine (i.e., customized treatment) and precision medicine (i.e., using genetic and molecular profiling) (see Chapter 8, "Personalized Medicine in Psychiatry," and Chapter 9, "Machine Learning in Psychopharmacology," in this textbook), inspired largely by interest in applying findings from the human genome project to devising treatments (mainly in oncology and infectious diseases) tailored to the genetic specifications of a single individual. There remains great debate about the commercial applicability of pharmacogenetics to psychiatry, where many factors other than genetics likely contribute to treatment outcomes, and most study findings thus far have been provisional and await replication. This section will address practical knowledge and implications of pharmacogenetic testing with respect to relevance for clinical practitioners.

Although the terms *pharmacogenetics* and *pharmacogenomics* are often used interchangeably, the former technically refers to single-gene variations that are thought to influence drug response, while the latter refers more broadly to the collective influence on drug effects of genetic variability across the entire genome. From among the roughly 20,000 genes in the human genome, those that code for functional proteins can have alterations in their nucleotide sequences that produce functional variants (called *single nucleotide polymorphisms*, or SNPs). Functional SNPs represent candidate genes that may be associated with proteins involved in drug metabolism or pharmacodynamic efficacy. Two main foci of interest have driven most pharmacogenetic investigations in psychiatry: 1) the identification of allelic variants in genes that code for catabolic enzymes involved in phase I or phase II metabolism (for which pharmacokinetic effects can influence delayed or hastened elimination, tolerability and adverse effects, and conversion of parent drugs to active metabolites) and 2) SNPs involved in candidate genes whose products exert specific pharmacodynamic effects, such as receptor targets or intermediary products in key biochemical (e.g., monoaminergic) pathways.

One of the key limitations in pharmacogenetic studies involves the fact that psychiatric genetics is almost always non-Mendelian, meaning that multiple genes of small effect are the contributors to observed phenotypes that represent complex traits. That in turn means that enormous statistical power is generally needed to identify the very small effects expected from genetic influences. Furthermore, the field has increasingly turned away from the concept of investigating single candidate genes and their potential associations with drug effects and instead endeavored to focus on genome-wide association studies (GWAS) for the sake of obtaining valid and replicable findings. Adequate sample sizes to provide sufficient power for GWAS (where *P* values generally must be less than 5 x $10^{[?]8}$) have not, as yet, been undertaken in any combinatorial pharmacogenetic studies in psychiatry.

Epigenetic Modifications

Epigenetic modifications refer to stable, reversible, heritable alterations in gene expression that occur without changes to an original DNA sequence. Posttranscriptional

modifications that can occur to DNA in response to psychotropic drug exposure constitute epigenetic events that can alter DNA accessibility or chromatin structure. The most prominent examples among these are DNA methylation or histone acetylation/deacetylation, as well as phosphorylation, deimination, ubiquitylation, SUMOylation (i.e., addition of small ubiquitin-related modifiers [SUMOs]), and adenosine diphosphate (ADP) ribosylation. The addition of methyl groups to cytosine residues of DNA (generally, cytosine-phosphate-guanine (CpG) dinucleotides, or CpG sites, often found in DNA promoter regions) *suppresses* gene expression by silencing genes and blocking the binding of transcription factors to promoter regions. Notably, animal models of depression identify increased methylation of brain-derived neurotrophic factor (BDNF), leading to reduced transcription and translation (Webb *et al.* 2020) that is, at least in principle, reversible by demethylation. In preclinical in vitro studies, astrocyte exposure to amitriptyline has been shown to produce DNA hypomethylation (Perisic *et al.* 2010). The SSRI escitalopram has been shown to reverse hypermethylation at a gene called *P11* (known also as the S100 calcium-binding protein A10 gene, or *S100A10*, a putative risk allele for depression) (Melas *et al.* 2012). However, studies of the effects of antidepressants more broadly on DNA methylation versus demethylation have also produced counterintuitive findings, with some reports identifying *hyper*methylation after antidepressant exposure at the BDNF promoter, and others reporting links between *hypo*methylation of monoamine oxidase A (MAO-A) and a *poorer* response to antidepressants. Methylation of sites within a number of candidate genes in addition to *BDNF*, including *SLC6A4*, *HTR1A*, *HTR1B*, *IL11*, and the whole genome, have been reported in association with antidepressant response (Webb *et al.* 2020). It remains uncertain whether such findings regarding methylation (versus demethylation) and antidepressant response represent truly conflicting results versus possible type I errors, or simply raise questions about the true role of suspected candidate genes, such as *BDNF*, and their regulation in MDD.

Histone acetylation refers to the addition of acetyl groups to lysine residues located on histones (basic proteins around which DNA is wound); acetylation allows greater interaction of DNA binding proteins with exposed chromatin strands, in turn upregulating gene transcription. Histone deacetylase inhibitors may represent an attractive strategy for understanding psychotropic drug effects at the molecular level. Divalproex, for example, has been shown to inhibit histone deacetylase (Phiel *et al.* 2001) among its varied known mechanisms of action.

Let us now consider more specifically the clinical relevance of pharmacogenetics separately with respect to pharmacokinetic versus pharmacodynamic aspects of psychopharmacology. It is worth first noting that despite enthusiasm from many commercial vendors of pharmacogenetic testing kits, regulatory agencies have expressed caution about the utility of ordering pharmacogenetic testing in a routine fashion with the hopes of predicting psychotropic drug response. Indeed, on October 31, 2018, the FDA issued a consumer safety warning regarding pharmacogenetic test results with respect to antidepressants. The FDA noted that "the relationship between DNA variations and the effectiveness of antidepressant medication has never been established" and suggested that "healthcare providers should not make changes to a patient's medication regimen based on results from genetic tests that claim to predict a patient's response to specific medications" (U.S. Food and Drug Administration 2018). Similarly, the American Psychiatric Association Council of Research Task Force

on Novel Biomarkers and Treatments concluded in 2018 that "at present, there are insufficient data to support the widespread use of combinatorial pharmacogenetic testing in clinical practice" but did note that testing may sometimes be informative for predicting some adverse drug events

(Zeier *et al.* 2018). Readers are advised to adopt a critical perspective when interpreting the available literature on both safety and efficacy pharmacogenetics, considering the methodological limitations described below, before extrapolating findings to direct patient care.

Pharmacokinetic Pharmacogenetics

Recall from earlier discussions that phase I and phase II catabolic enzymes are responsible for modifying drug substrates that undergo metabolism either to biologically active metabolites or to products eliminated from the body. Known genetic variants that code for pharmacokinetic enzymes may contribute to the efficiency or inefficiency of drug metabolism by producing genotypes (metabolic enzymes) that are normal (called "extensive metabolizers," or EMs), overactive (called "ultrarapid metabolizers," or URMs), or inefficiently slow (called "poor metabolizers," or PMs). Drugs that are substrates for phase I or phase II enzymes in URM or PM genotype patients may have impaired responses due to hastened metabolism or delayed drug clearance (and consequent greater side-effect burden), respectively. While commercially available pharmacogenetic testing protocols tend to advise the all-or-none avoidance of drugs that are metabolized by specific catabolic enzymes in PMs or URMs, another clinical approach would be to anticipate the need for lower-than-usual dosing of a drug that is a substrate for an enzyme with the PM genotype, or to consider ostensibly supratherapeutic dosing of specific drugs metabolized by enzymes with URM genotypes. More absolute contraindications to using a drug in a PM genotype patient would be those for which conversion from a prodrug to an active metabolite is precluded, as in the case of conversion of tamoxifen to endoxifen via CYP2D6 (i.e., for the same reasons that tamoxifen should not be coprescribed with potent 2D6 inhibitory drugs such as paroxetine, fluoxetine, and duloxetine, as listed in Table 6-2).

TABLE 6-2. Cytochrome P450 (CYP) metabolizer subtypes with known inhibitors and inducers

Enzyme	Ultrarapid metabolizer frequency	Poor metabolizer frequency	Inhibitors	Inducers
CYP2D6	Whites: 4%	Whites: 6%-10%	Bupropion	None
	Blacks: 5% (Ethiopians: 29%)	Blacks: 2%-7% (South African Blacks: 29%)	Citalopram	
	Asians: 1%	Asians: 0%-2%	Doxepin	
	Hispanics: 1%-2%	Hispanics: 2%-6%	Duloxetine	
			First-generation antipsychotics (most)	

Source. Adapted from Table 2-6 (p. 70) in Goldberg JF, Ernst CL: *Managing the Side Effects of Psychotropic Medications*, 2nd Edition. Washington, DC, American Psychiatric Association Publishing, 2019. Copyright (c) 2019, American Psychiatric Association. Used with permission.

Enzyme	**Ultrarapid metabolizer frequency**	**Poor metabolizer frequency**	**Inhibitors**	**Inducers**
			Fluoxetine	
			Fluvoxamine (weak)	
			Imipramine	
			Moclobemide	
			Paroxetine	
			Risperidone	
			Sertraline (moderate)	None
			Tranylcypromine (moderate)	
			Vilazodone	None
CYP1A2	Not well characterized	Not well characterized	Fluvoxamine	(Ar)modafinil
			Moclobemide	
			Tranylcypromine (moderate)	
CYP3A4/5	Not well characterized	Whites: 5%	Escitalopram (weak)	(Ar)modafinil
			Fluvoxamine	Carbamazepine
			Nefazodone	Oxcarbazepine
CYP2C19	Not well characterized	Whites: 3%-5%	Amitriptyline	St. John's wort
		Blacks: 4%	(Ar)modafinil	
		Asians: 15%-20%	Carbamazepine (weak)	
			Clomipramine	
			Desipramine (weak)	
			Fluoxetine	
			Fluvoxamine	
			Imipramine	
			Moclobemide	
			Oxcarbazepine	
			Topiramate (weak)	

Source. Adapted from Table 2-6 (p. 70) in Goldberg JF, Ernst CL: *Managing the Side Effects of Psychotropic Medications*, 2nd Edition. Washington, DC, American Psychiatric Association Publishing, 2019. Copyright (c) 2019, American Psychiatric Association. Used with permission.

Enzyme	Ultrarapid metabolizer frequency	Poor metabolizer frequency	Inhibitors	Inducers
			Tranylcypromine (moderate) Vilazodone	

Source. Adapted from Table 2-6 (p. 70) in Goldberg JF, Ernst CL: *Managing the Side Effects of Psychotropic Medications*, 2nd Edition. Washington, DC, American Psychiatric Association Publishing, 2019. Copyright (c) 2019, American Psychiatric Association. Used with permission.

Notably, a relatively small proportion of the population has either URM or PM genotypes at loci for catabolic enzymes, and those proportions stratify across racial-ethnic groups. Pharmacogenetic studies therefore must account for possible racial-ethnic-geographic population stratification when reporting findings across subject groups. Known allele frequencies for URMs and PMs across several CYP isoenzymes involved in psychotropic drug metabolism, with examples of known drug inhibitors and inducers, are summarized in Table 6-2.

Several antidepressants (specifically, citalopram, escitalopram, venlafaxine, tertiary amine tricyclics) also are substrates for *P-glycoprotein*, a cell membrane protein encoded by the gene *ABCB1* that transports xenobiotics across the blood-brain barrier. Some studies have found that higher antidepressant doses may be needed to exert therapeutic effects in "G" allele carriers at the *ABCB1* 2677 G > T SNP, although conflicting findings have also been reported (Wolking *et al.* 2015).

With respect to pharmacogenetic variants of phase II metabolic enzymes, several examples are noteworthy. Valproic acid and lamotrigine are both metabolized via UDP-glucuronosyltransferase (UGT) glucuronidation. In the case of divalproex, several candidate genes have been preliminarily studied, including *UGT1A3*, *UGT1A4*, *UGT1A6*, *UGT1A8*, *UGT1A9*, *UGT1A10*, *UGT2B7*, and *UGT2B15* (Krishnaswamy *et al.* 2005). With respect to lamotrigine, variants of *UGT1A4* and *UGT2B7* have been studied in relation to drug concentration-to-dose ratios (CDRs). Known SNPs of *UGT1A4* (i.e., 70 C > A or 142 T > G) have not been shown to influence lamotrigine CDRs, but homozygotes for the *UGT2B7* -161 C > T polymorphism have been shown to produce higher lamotrigine CDRs than are seen among heterozygotes or wild types (Kim and Kim 2019).

Despite speculation that PMs would be expected to incur an overabundance of adverse drug effects, the empirical literature in this area, though sparse, has not been especially compelling. In MDD, one of the largest randomized trials conducted to date (the Genomics Used to Improve DEpression Decisions [GUIDED] study), found that, contrary to expectations, MDD patients randomly assigned to treatment informed by a combinatorial pharmacogenetics panel did not differ from MDD patients who received treatment as usual (TAU) in their mean number of antidepressant drug side effects (0.243 vs. 0.237, $P = 0.885$) or the proportion of subjects who experienced side effects (about 15% in both the pharmacogenetically guided arm and TAU)

(Greden *et al.* 2019). However, subjects whose medications were switched to pharmacogenetically congruent options subsequently had significantly fewer adverse effects as compared to those who did not.

On the other hand, certain adverse effects have been shown to demonstrate more compelling associations with specific genes or risk alleles. From among the examples listed in Table 6-3, perhaps the most well recognized is the association between the gene *HLA-B*1502* and the risk for developing Stevens-Johnson syndrome after exposure to carbamazepine in individuals of Southeast Asian descent. In fact, the manufacturer's product labeling for carbamazepine carries a boxed warning that requires assessment for the presence of this gene before prescribing carbamazepine to at-risk individuals. Another example of compelling data for the use of pharmacogenetic testing for safety purposes involves the recognition of CYP2D6 PMs for whom drugs may be prescribed that can cause QT prolongation on electrocardiogram. Iloperidone, for example, includes language in its manufacturer's product label stating that dosage "should be reduced in patients who are poor metabolizers of CYP2D6." The manufacturers' product labeling for most tricyclic antidepressants also includes language warning of the risk for higher drug plasma levels among patients with PM genotypes for CYP2D6.

TABLE 6-3. Pharmacogenetic correlates of psychotropic adverse effects

Adverse effect	**Risk allele or genotype**
Severe cutaneous reactions (carbamazepine)	*HLA-B*1502* (risk for Stevens-Johnson syndrome) in Han Chinese/Malaysians
*HLA-A*3101* (risk for Stevens-Johnson syndrome) in Japanese/European populations	
Sexual dysfunction (SSRIs)	*GRIA3*, *GRIK2*, *GR1A1*, *GRIN3A*, *GRIA2*
5HT2A -1438 G/A ("GG" homozygosity)	
Sialorrhea (clozapine)	*DRD2* 120-bp tandem repeat sequence
SSRI-associated mania	*SLC6A4* "s" allele
Tardive dyskinesia (FGAs, SGAs)	*HSPG2* ("G" allele), *DPP6* (rs6977820), *SLC18A2* ("C" allele), *PIP5K2A*, *CNR1* (rs806374 "C" allele) (Lanning *et al.* 2018); *CYP26* PMs or URMs (Lu *et al.* 2020); *DRD3* (Ser - Gly SNP at exon 1)
Weight gain (SGAs)	*ADRB3* (Arg/Arg homozygosity)
	5HT2C -759 C/T ("CC" homozygosity); *5HT2C* Cys23/Ser23 (23Cys = risk)
	BDNF (Val^{66}Met)
	DRD2 ("A" allele = risk)
	5HTR2A 102 T/C ("CC" homozygosity)
	LEP -2548 A/G ("G" allele)

Adverse effect	Risk allele or genotype
	MTHFR 677 C/T ("CC" homozygosity)
	GNB3 (C825T variant)

Note. Arg = Arginine; bp = base pair; Cys = Cysteine; FGAs = first-generation antipsychotics; Gly = glycine; PM = poor metabolizer; Ser = serine; SGAs = second-generation antipsychotics; SNP = single nucleotide polymorphism; SSRI = selective serotonin reuptake inhibitor; URM = ultrarapid metabolizer.

Genes listed (and corresponding gene products): *ADRB3* (b-3 adrenergic receptor); *BDNF* (brain-derived neurotrophic factor); *CNR1* (cannabinoid receptor 1); *CYP26* (cytochrome P450 family 26 subfamily A member 1); *DPP6* (dipeptidyl peptidase like 6); *DRD2* (D_2 dopamine receptor); *DRD3* (D_3 dopamine receptor); *5HT2A* (5-hydroxytryptamine receptor 2A); *5HT2C* (5-hydroxytryptamine receptor 2C); *GNB3* (guanine nucleotide binding protein); *GRIA1*, *GRIA2*, and *GRIA3* (glutamate ionotropic receptor AMPA type subunits 1, 2, and 3); *GRIK2* (glutamate ionotropic receptor kainite type subunit 2); *GRIN3A* (glutamate ionotropic receptor NMDA type subunit 3A); *HLA-A* and *HLA-B* (major histocompatibility complex classes 1A and 1B); *HSPG2* (heparan sulfate proteoglycan 2); *LEP* (leptin); *MTHFR* (methylene tetrahydrofolate reductase); *PIP5K2A* (phosphatidylinositol-4-phosphate 5-kinase type II a); *SLC6A4* (solute carrier family 6, member 4 [serotonin transporter]); *SLC18A2* (solute carrier family 18, member A2 [vesicular monoamine transporter 2]).

Source. Adapted from Table 2-8 (p. 75) in Goldberg JF, Ernst CL: *Managing the Side Effects of Psychotropic Medications*, 2nd Edition. Washington, DC, American Psychiatric Association Publishing, 2019. Copyright (c) 2019, American Psychiatric Association. Used with permission.

Pharmacodynamic Pharmacogenetics

More uncertainty and debate revolve around the use of routine pharmacogenetic testing to predict psychotropic drug efficacy. Some aspects of drug efficacy become intuitively obvious when considering the pertinent metabolic pathways of particular drugs, especially those whose biological activity is dependent on conversion from a prodrug to an active compound or an active metabolite. For example, venlafaxine depends on CYP2D6 for conversion to its primary active metabolite, desvenlafaxine. This process will be anything but efficient in CYP2D6 PMs, effectively rendering venlafaxine an inactive compound in PMs because of the blockade in its metabolic pathway. Carbamazepine is essentially a prodrug that must be converted by CYP3A4 to carbamazepine-10,11-epoxide (which may not occur in CYP3A4 PMs). Risperidone must be converted to its primary active metabolite, 9-hydroxyrisperidone (otherwise known commercially as paliperidone), primarily via CYP2D6, although because CYP3A4/5 provides a secondary degradative pathway for risperidone, it is possible that a CYP2D6 PM might nevertheless spare *some* buildup of the parent compound. It is worth noting here the observation made by Macaluso and Preskorn (2018) that simply by avoiding antidepressants and antipsychotics that undergo oxidative metabolism, clinicians can most of the time replicate the same "binned" recommendations made by most pharmacogenetic testing protocols. One might add that pharmacokinetic candidate genes have little if any relevance for drugs that are metabolized by multiple metabolic pathways (see appendix to this chapter) or those that undergo no biotransformation before being eliminated.

Studies of combinatorial pharmacogenetics designed to predict symptom improvement, response, and remission have been conducted in mainly a preliminary fashion in MDD, schizophrenia, and a handful of other conditions such as ADHD, and for most existing provisional findings, the field lacks replication studies (much less those with adequate statistical power). Initial open, nonrandomized trials in MDD were criticized for failing to account for expectancy bias among pharmacogenetic recipients (meaning that patients and providers were both aware that a specialized type of treatment would be occurring). The aforementioned GUIDED trial--a blinded randomized trial--failed to show a significant advantage for pharmacogenetically informed care over TAU for MDD on the primary outcome (change in symptom reduction) (Greden *et al.* 2019). A series of post hoc analyses from that database showed a nominally significant advantage for pharmacogenetically guided care for achieving "response" (26% with pharmacogenetics vs. 19.9% with TAU) and "remission" (15.3% with pharmacogenetics vs. 10.1% with TAU), producing a small magnitude of effect (number needed to treat [NNT] = 17 for response and 19 for remission) (Goldberg *et al.* 2019).

There now exist a large number of candidate genes that have been studied for possible associations with pharmacodynamic efficacy, mostly in the case of antidepressant or antipsychotic response to pharmacotherapies in MDD and schizophrenia, respectively. Some are of mainly theoretical relevance to concepts such as neuroprotection (e.g., the *BDNF* Val^{66} polymorphism) or are linked with enzymes or intermediary products in the synthesis of monoaminergic neurotransmitters (e.g., *TPH2* [tryptophan hydroxylase] for production of serotonin); still others are candidate gene polymorphisms involved in protein synthesis for ion channels (e.g., *CACNA1C* and the calcium channel) or neurotransmitter receptors (e.g., *DRD4* variants and the dopamine D$_4$ receptor; *SLC6A4* variants and the serotonin transporter gene).

It is often a matter of speculation as to whether known polymorphisms of genes such as these meaningfully and reliably produce observable pharmacodynamic effects. For example, consider the degradation of dopamine via catechol-O-methyltransferase (COMT), for which a known polymorphism (Val^{158}Met, also known as rs4680) produces a high activity (Val/Val) and a low activity (Met/Met) variant. Low-activity variants, in principle, lead to less degradation of dopamine, which could have implications for attentional processing in disorders such as schizophrenia or ADHD. One commercial pharmacogenetics company directs prescribers to favor nonstimulant treatment options for ADHD in patients homozygous for Met/Met (low activity) rs4680, based on the hypothesis that a dopamine agonist may be less effective in such patients. Is this evidence-based? A meta-analysis examining methylphenidate response vis-a-vis COMT genotype identified seven studies (five of which had nonsignificant confidence intervals) that collectively revealed a statistically significant 40% increased chance of response in Val/Val homozygotes (Myer *et al.* 2018). How does this finding generalize to predict the utility of stimulants in children with ADHD, relative to other factors associated with treatment outcome, such as IQ, age, severity, or concurrent anxiety (Buitelaar *et al.* 1995)? Does it extrapolate to adults with ADHD? Does it pertain to use of amphetamine as well as methylphenidate? (A Medline search reveals no pharmacogenetics studies specifically examining the COMT polymorphism and amphetamine response but conflicting findings regarding neurocognitive performance among healthy adults given D-amphetamine, stratified by COMT genotype.) Perhaps most importantly, is there evidence of better response to nonstimulant treatments for ADHD (e.g., atomoxetine) in rs4680 Met/Met homozygotes? (A Medline search revealed no studies examining this question.) These are among the key unanswered questions that stand between the bench and the bedside in relation to translating pharmacogenetics into a "ready for prime time" commercial enterprise.

Similar unknowns and caveats bear on existing candidate gene studies in relation to predicting antidepressant response in MDD. From among the many dozens of candidate genes that have been studied in exploratory fashion relative to antidepressant response, several have received particular attention. Particular interest has coalesced around the potential association between antidepressant response and the presence of short (s) versus long (l) allelic variants of the serotonin transporter gene polymorphism (locus *SLC6A4*). Carriers of the long variant (and, in particular, the L_A subtype) produce more serotonin transporter protein than do carriers of the short variant, or those with the L_G long variant--a consequence that, at least in principle, could predispose to a better response to SSRIs. A meta-analysis of 16 SSRI trials found an overall 1.7-fold greater likelihood of SSRI antidepressant response among l/l homozygotes than among s/s homozygotes, but that finding applied only to older white women with late age at onset of depression (Porcelli *et al.* 2012).

Another candidate gene of high interest in predicting antidepressant outcomes encodes methylene tetrahydrofolate reductase (MTHFR), with a known functional polymorphism associated with low enzyme activity. MTHFR catalyzes methylation of folic acid, facilitating its transfer across the blood-brain barrier. The low-activity variant of this enzyme (associated with the T allele at the 677 C > T polymorphism) should, in principle, bear clinical relevance for the subgroup of depressed patients especially likely to respond to supplemental dietary L-methylfolate. However, the sole empirical study testing this otherwise compelling hypothesis found a numerically favorable but statistically nonsignificant advantage for adjunctive L-methylfolate (dosed at 15 mg/day) in improving response rates among T allele carriers (23.1%) versus CC homozygotes (16.4% response) (Papakostas *et al.* 2014). If there is a true difference in L-methylfolate antidepressant response based on MTHFR genotype, the effect is likely a small one.

In schizophrenia, a review of 44 studies examining pharmacogenetic correlates of antipsychotic response found the strongest associations with CYP2D6 metabolizer genotype (Yoshida and Muller 2020). Association studies involving variants of the dopamine receptor gene (*DRD2*) and the 5-HT$_{2A}$ receptor gene (*HTR2A*) have produced more inconsistent findings. Six of nine studies in that review reported a significant association between antipsychotic response and the COMT Val^{158}Met polymorphism (rs4680); two of three studies reported significant associations with the *HTR2A* polymorphism (rs6314), along with several variants of *HTR2C*, and the type-7 metabotropic glutamate receptor gene (*GRM7*). GWAS also have identified a number of candidate genes potentially associated with antipsychotic response, including the genes for multiple EGF-like domains 10 (*MEGF10*); solute carrier family 1, member 1 (*SLC1A1*); protocahedrin 7 (*PCDH7*); contactin-associated protein-like 5 (*CNTNAP5*); TRAF2 and NCK-interacting kinase (*TNIK*); glutamate ionotropic receptor delta type subunit 2 (*GRID2*); and erb-b2 receptor tyrosine kinase 4 (*ERBB4*).

In bipolar disorder, lithium response has been described preliminarily in association with a handful of candidate genes, including *PLCG-1*, *GSK3* ("C" allele associated with response), *XBP1*

("C" allele associated with response), and *NTRK2* ("TT" homozygosity associated with response), as well as mtDNA (Pagani *et al.* 2019).

Replication is needed across essentially all of the aforementioned studies before meaningful recommendations can be made to psychiatrists, who may be eager to embrace pharmacogenetic markers as useful tools for everyday clinical practice.

Table 6-4 summarizes the pros and cons of pharmacogenetic testing for practitioners.

TABLE 6-4. Pros and cons of pharmacogenetic testing in clinical practice

Pros	Cons
Testing provides safety information about specific at-risk groups (e.g., *HLA-B*1502* and Stevens-Johnson syndrome in Southeast Asians; risk for QTc prolongation in poor metabolizer genotypes for cytochrome P450 [CYP] substrates that can prolong QTc).	No robust data exists to predict drug efficacy or response in any psychiatric disorder.
Clinicians can affirm clinical suspicions about lack of efficacy for poor metabolizers of CYP substrates who cannot convert parent drugs to their active metabolites (e.g., venlafaxine and CYP2D6; carbamazepine and CYP3A4; risperidone and CYP2D6), or ultrarapid metabolizers who may need supratherapeutic dosages to achieve efficacy.	The extent to which genetic factors contribute to drug response relative to clinical and other nongenetic determinants is not yet fully understood.
Pharmacogenetic correlates of specific adverse effects (e.g., metabolic dysregulation) may be useful in anticipating specific drug tolerabilities--though current technology does not allow reliable prediction of serious adverse events such as iatrogenic agranulocytosis.	Drug nonresponse due to ultrarapid metabolizer genotypes, or excessive side effects, can be predicted and thus averted by choosing drugs that undergo different metabolic pathways, without necessity of pharmacogenetic testing.
	Single candidate gene strategies appear technologically inferior to genome-wide association studies--but findings from the latter are scant and not replicated.
	Current pharmacogenetic studies often do not systematically account for population stratification and variation in allele frequencies across racial-ethnic-geographic groups, limiting the generalizability of findings.
	Misleading recommendations from pharmacogenetic testing have been reported that contradict clinical observations (e.g., disputed value of a clozapine trial in treatment-resistant schizophrenia) (Rahman *et al.* 2017).

Pros	Cons
	Cost-effectiveness has not yet been demonstrated in replicated findings (Rosenblat *et al.* 2017).

Conclusion

Expert psychopharmacology involves a strong working knowledge of the basic concepts behind pharmacokinetics and pharmacodynamics. It is probably not so useful or important for clinicians to attempt to memorize every CYP enzyme-substrate pairing, the particular dissociation constants of ligand-receptor binding configurations, the magnitude by which bioavailability diminishes after a drug undergoes first-pass metabolism, or the specific data to support or refute the utility of specific pharmacogenetic SNPs. They should instead focus on understanding how to interpret data in these areas, and how to make use of lifelong educational resources, as the field continues to expand in technology and depth of information.

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APPENDIX

Pharmacokinetic Parameters of Specific Medications

First-generation antipsychotics

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Chlorpromazine	10%-80%	None	30 hours	CYP2D6	No
Fluphenazine	2.7%	None	15-30 hours	Presumed to be CYP2D6	No
Haloperidol	60%-70%	None	14.5-36.7 hours	Glucuronidation, CYP3A4, CYP1A2	No
Perphenazine	40%	None	9-12 hours	CYP2D6	No
Pimozide	50%	None	29-150 hours	CYP3A4 (primary); CYP1A2 (minor)	No
Thioridazine	50%	None	7-13 hours	CYP2D6	No
Thiothixene	Unknown	None	10-20 hours	CYP2D6	No
Trifluoperazine	100%	None	12.5-13.6 hours	CYP1A2	No

Note. CYP = cytochrome P450.

Second-generation antipsychotics

Agent	**Oral bioavailability**	**Effect of food with oral administration**	**Half-life ($t_{1/2}$)**	**Primary metabolic pathway**	**Renal dosing required?**
Aripiprazole	87%	None	75 hours	CYP2D6, CYP3A4	No
Asenapine	< 2% (oral); 35% (sublingual)	Should not be swallowed[a]	24 hours	CYP1A2; UGT1A4	No
Brexpiprazole	95%	None	91 hours	CYP2D6, CYP3A4	Yes
Cariprazine	52%	None	48-96 hours[b]	CYP3A4 (primary); CYP2D6 (minor)	No
Clozapine	60%-70%	Food lowers C_{max} by 20%	14 hours	CYP1A2, CYP3A4 (primary); CYP2C19, CYP2D6 (minor)	No
Iloperidone	36%	None	18 hours	CYP2D6, CYP3A4	No
Lumateperone	4.4%	High-fat food lowers C_{max} by 33% and increases AUC by 9%	13-18 hours	UGT1A1, UGT1A4, UGT2B15; aldo-keto reductase 1C1, 1B10, 1C4; CYP 3A4, CYP2C8, CYP1A2	No
Lurasidone	9%-19%	[?] 350-calorie meal increases C_{max} threefold	18 hours	CYP3A4	Yes
Olanzapine	60%-65%	None	33 hours	CYP1A2 (primary); CYP2D6, UGT1A4 (minor)	No

Note. AUC = area under the curve; C_{max} = maximum concentration; CYP = cytochrome P450; IR = immediate release; UGT = uridine diphosphate [UDP]-glucuronosyltransferase; XR = extended release.

[a] Manufacturer advises not eating or drinking for 10 minutes after sublingual administration.

[b] Cariprazine has two active metabolites, each with relatively long half-lives: desmethylcariprazine ($t_{1/2}$ = 24-48 hours) and didesmethylcariprazine ($t_{1/2}$ = 1-3 weeks).

Agent	**Oral bioavailability**	**Effect of food with oral administration**	**Half-life ($t_{1/2}$)**	**Primary metabolic pathway**	**Renal dosing required?**
Paliperidone	28%	None	3-17 hours	Mostly renally excreted unmetabolized; some metabolism by CYP3A4 and P-glycoprotein 274	Yes
Quetiapine	100%	IR: none XR: food increases C_{max} by about half; manufacturer recommends ingestion on empty stomach or with only a light meal	6 hours	CYP3A4	No
Risperidone	70%	None	3 hours	CYP2D6	Yes
Ziprasidone	50% (with food)	Greater absorption with food ([?] 500 calories)	6-7 hours	CYP3A4; aldehyde oxidase	No

Note. AUC = area under the curve; C_{max} = maximum concentration; CYP = cytochrome P450; IR = immediate release; UGT = uridine diphosphate [UDP]-glucuronosyltransferase; XR = extended release.

[a] Manufacturer advises not eating or drinking for 10 minutes after sublingual administration.

[b] Cariprazine has two active metabolites, each with relatively long half-lives: desmethylcariprazine ($t_{1/2}$ = 24-48 hours) and didesmethylcariprazine ($t_{1/2}$ = 1-3 weeks).

Monoaminergic antidepressants

Agent	**Oral bioavailability**	**Effect of food with oral administration**	**Half-life ($t_{1/2}$)**	**Primary metabolic pathway**	**Renal dosing required?**

Note. AUC = area under the curve; C_{max} = maximum concentration; CrCl = creatinine clearance; CYP = cytochrome P450; 5-HT = 5-hydroxytryptamine (serotonin); MAOIs = monoamine oxidase inhibitors; NaSSAs = noradrenergic and specific serotonergic antidepressants; NDRI = norepinephrine-dopamine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants; T_{max} = time to peak drug concentration.

[a] Not available in the United States.

[b] Food increases the bioavailability of trazodone but also prolongs time to its peak plasma concentration; when used off-label to treat insomnia, prolonged T_{max} due to ingestion with food may therefore be undesirable.

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Azapirone					
Gepirone	14%-17%	Increases AUC but not C_{max} or T_{max}	5 hours	CYP3A4	Only if CrCl < 50 mL/minute
SSRIs					
Citalopram	80%	None	35 hours	CYP3A4, CYP2C19	Only if CrCl < 30 mL/minute
Escitalopram	80%	None	27-32 hours	CYP2D6, CYP2C19	No data when CrCl < 30 mL/minute
Fluoxetine	60%-80%	None	4-6 days (norfluoxetine: 7-9 days)	CYP2D6	No
Fluvoxamine	50%	None	15-20 hours	CYP2D6, CYP1A2	No data
Paroxetine	30%-60%	None	21 hours	CYP2D6	Only if CrCl<30 mL/minute
Sertraline	44%	None	26 hours	CYP2B6 (primary); CYP2D6, CYP2A4, CYP2C19 (minor)	None

Note. AUC = area under the curve; C_{max} = maximum concentration; CrCl = creatinine clearance; CYP = cytochrome P450; 5-HT = 5-hydroxytryptamine (serotonin); MAOIs = monoamine oxidase inhibitors; NaSSAs = noradrenergic and specific serotonergic antidepressants; NDRI = norepinephrine-dopamine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants; T_{max} = time to peak drug concentration.

[a] Not available in the United States.

[b] Food increases the bioavailability of trazodone but also prolongs time to its peak plasma concentration; when used off-label to treat insomnia, prolonged T_{max} due to ingestion with food may therefore be undesirable.

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
SNRIs					
Desvenlafaxine	80.5%	None	10 hours	UGT1A1	Yes 276
Duloxetine	50%	None	12 hours	CYP2D6, CYP1A2	Only if CrCl < 30 mL/minute
Levomilnacipran	92%	None	12 hours	CYP3A4 (primary); CYP2D6, CYP3A4, CYP2C19, CYP2C8, CYP2J2 (minor)	Only if CrCl<60 mL/minute
Venlafaxine	45%	Food decreases rate but not extent of absorption	4 hours	CYP2D6	Yes
MAOIs					
Isocarboxazid	Not established	None (but must follow tyramine-free diet)	1.5-4 hours	Not fully understood; possible *N*-acetylation	No
Moclobemide	60%-80%	Slightly decreased absorption (T_{max} decreased by about 40 minutes) with food	2-4 hours	CYP2C19, CYP2D6	No 277

Note. AUC = area under the curve; C_{max} = maximum concentration; CrCl = creatinine clearance; CYP = cytochrome P450; 5-HT = 5-hydroxytryptamine (serotonin); MAOIs = monoamine oxidase inhibitors; NaSSAs = noradrenergic and specific serotonergic antidepressants; NDRI = norepinephrine-dopamine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants; T_{max} = time to peak drug concentration.

[a] Not available in the United States.

[b] Food increases the bioavailability of trazodone but also prolongs time to its peak plasma concentration; when used off-label to treat insomnia, prolonged T_{max} due to ingestion with food may therefore be undesirable.

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Phenelzine	Not well established	None (but must follow tyramine-free diet)	11.6 hours	Oxidized to phenylacetic acid and parahydroxyphenyl-acetic acid; acetylation to *N*^{2}-acetylphenelzine is a minor pathway	No
Selegiline transdermal	73%	No pharmacokinetic effect; must follow tyramine-free diet at dosage of 9 mg/day or 12 mg/day	18-25 hours	CYP2B6, CYP2C9, CYP3A4	No
Tranylcypromine	50%	None (but must follow tyramine-free diet)	2 hours	Metabolized via ring hydroxylation and *N*-acetylation; the role of specific metabolic enzymes is not well understood	No
NaSSAs					
Mianserin[a]	20%-30%	None	21-61 hours	CYP2D6, CYP2B6	No
Mirtazapine	50%	None	20-40 hours	CYP2D6, CYP3A4, CYP1A2	Yes if CrCl < 40 mL/minute

Note. AUC = area under the curve; C_{max} = maximum concentration; CrCl = creatinine clearance; CYP = cytochrome P450; 5-HT = 5-hydroxytryptamine (serotonin); MAOIs = monoamine oxidase inhibitors; NaSSAs = noradrenergic and specific serotonergic antidepressants; NDRI = norepinephrine-dopamine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants; T_{max} = time to peak drug concentration.

[a] Not available in the United States.

[b] Food increases the bioavailability of trazodone but also prolongs time to its peak plasma concentration; when used off-label to treat insomnia, prolonged T_{max} due to ingestion with food may therefore be undesirable.

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Nefazodone	20%	None	2-4 hours	CYP3A4	No
Trazodone	65%-80%	See comment[b]	10-12 hours	CYP3A4	No
NDRI					
Bupropion	80%-90%	None	21 hours (with chronic dosing)	CYP2B6	No
5-HT modulators					
Vilazodone	72% with food	Food increases C_{max}, AUC about twofold	25 hours	CYP3A4 (primary); CYP2C19, CYP2D6 (minor)	No
Vortioxetine	75%	None	66 hours	CYP2D6 (primary); CYP3A4, CYP2C19, CYP2C8, CYP2C9, CYP2A6, CYP2B6 (minor)	
TCAs ***Secondary amines***					
Desipramine	30%-55%	None	12-54 hours	CYP2D6 (primary); CYP1A2 (minor)	No
Nortriptyline	51%	None	26 hours	CYP2D6	No
Maprotiline	50%	None	51 hours	CYP2D6, CYP1A2	No
Tertiary amines					

Note. AUC = area under the curve; C_{max} = maximum concentration; CrCl = creatinine clearance; CYP = cytochrome P450; 5-HT = 5-hydroxytryptamine (serotonin); MAOIs = monoamine oxidase inhibitors; NaSSAs = noradrenergic and specific serotonergic antidepressants; NDRI = norepinephrine-dopamine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants; T_{max} = time to peak drug concentration.

[a] Not available in the United States.

[b] Food increases the bioavailability of trazodone but also prolongs time to its peak plasma concentration; when used off-label to treat insomnia, prolonged T_{max} due to ingestion with food may therefore be undesirable.

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Amitriptyline	6%	None	21.7 hours	CYP1A2, CYP2D6, CYP2C19	No
Clomipramine	50%	None	24 hours; for active metabolite dimethyl-clomipramine = 96 hours	2C19, CYP1A2, CYP3A4 and *N*-demethylation	No
Doxepin	29%	Food delays absorption	8-25 hours	CYP2C19, CYP2D6 (primary); CYP1A2, CYP2C9 (minor)	No
Imipramine	29%-77%	None	6-20 hours	CYP2D6, CYP3A4, CYP1A2, CYP2C9	No
Trimipramine	41%	None	8-24 hours	CYP2D6, CYP2C19, CYP2C9	No

Note. AUC = area under the curve; C_{max} = maximum concentration; CrCl = creatinine clearance; CYP = cytochrome P450; 5-HT = 5-hydroxytryptamine (serotonin); MAOIs = monoamine oxidase inhibitors; NaSSAs = noradrenergic and specific serotonergic antidepressants; NDRI = norepinephrine-dopamine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants; T_{max} = time to peak drug concentration.

[a] Not available in the United States.

[b] Food increases the bioavailability of trazodone but also prolongs time to its peak plasma concentration; when used off-label to treat insomnia, prolonged T_{max} due to ingestion with food may therefore be undesirable.

Lithium and anticonvulsants

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Carbamazepine	75%-85%	None	25-65 hours	3A4	No
Divalproex	Divalproex DR = 100%;	Food slows rate of absorption	9-16 hours	Glucuronidation and mitochondrial b-oxidation	No

Note. AUC = area under the curve; CYP = cytochrome P450; DR = delayed release; ER = extended release; UDP = uridine diphosphate.

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
	divalproex ER = 89%			(primary); CYP2A6, CYP2B6, CYP2C9, CYP3A5 (minor)	
Gabapentin	27%-60%	None	5-7 hours	None	Yes
Gabapentin enacarbil	75%	30%-40% greater exposure (AUC) with food	5.1-6 hours	None	Yes
Lamotrigine	98%	None	25-33 hours	UDP-glucuronidation	No
Lithium	100%	None	24 hours	None	Yes
Oxcarbazepine	> 95%	None	2 hours (active 10-monohydroxy metabolite = 10 hours)	CYP3A4	Yes
Topiramate	27%-59%	None	21 hours	CYP3A4	Yes
Zonisamide	100%	None	63 hours	CYP3A4	No

Note. AUC = area under the curve; CYP = cytochrome P450; DR = delayed release; ER = extended release; UDP = uridine diphosphate.

Stimulants and related drugs for ADHD

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Atomoxetine	63%	None	5.2 hours (21.6 hours in CYP2D6 poor	CYP2D6	No

Note. AUC = area under the curve; C_{max} = maximum concentration; CrCl = creatinine clearance; CYP = cytochrome P450.

[a] Food speeds absorption of immediate-release methylphenidate. Ingestion of extended-release methylphenidate with versus without food does not affect absorption.

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
			metabolizers)		
Dextroamphetamine	75%-100%	None	10-12 hours	CYP2D6	No
Guanfacine	80%	None	17 hours	CYP3A4	No
Lisdexamfetamine	> 75%	Same AUC with or without food but lower C_{max} with food	12 hours	Hydrolyzed in blood to D-amphetamine	No
Methylphenidate	11%-52%	See comment[a]	2-3 hours	Hepatic carboxylesterase 1 (*CES1A1*) metabolizes methylphenidate to ritalinic acid	No
(Ar)modafinil	80% modafinil; 98% armodafinil	None	13-15 hours (modafinil); 15-20 hours (armodafinil)	Amide hydrolysis; CYP3A4, CYP2C19	No data when CrCl < 30 mL/minute
Solriamfetol	95%	None	7.1 hours	Largely excreted unmetabolized	Yes if CrCl < 60 mL/minute

Note. AUC = area under the curve; C_{max} = maximum concentration; CrCl = creatinine clearance; CYP = cytochrome P450.

[a] Food speeds absorption of immediate-release methylphenidate. Ingestion of extended-release methylphenidate with versus without food does not affect absorption.

Sedative-hypnotics and related anxiolytics

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Benzodiazepines					

Note. CYP = cytochrome P450; T_{max} = time to peak drug concentration.

[a] Oxazepam and temazepam are active metabolites of diazepam.

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Alprazolam	90%	None	11 hours	CYP3A4	No
Chlordiazepoxide	100%	None	5-30 hours	CYP3A4 (oxidation), then glucuronidation	No
Clonazepam	90%	None	30-40 hours	CYP3A4	No
Diazepam	94%	None	51 hours	CYP3A4, CYP2C19 (*N*-demethylated); metabolites are oxidated (CYP3A4) and glucuronidated	No
Lorazepam	90%	None	12 hours	Glucuronidation	No
Oxazepam[a]	93%	None	6-9 hours	Glucuronidation	No
Temazepam[a]	96%	None	10 hours	Glucuronidation	No
Benzodiazepine agonists					
Eszopiclone	80%	Food slows absorption	7 hours	CYP3A4	No
Zaleplon	30%	Food slows absorption	1 hour	Aldehyde oxidase; minor: CYP3A4	No
Zolpidem	67%	Food slows absorption	1 hour	CYP3A4; minor: CYP1A2, CYP2C9	No

Note. CYP = cytochrome P450; T_{max} = time to peak drug concentration.

[a] Oxazepam and temazepam are active metabolites of diazepam.

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Orexin antagonists					
Lemborexant	87%	Food delays T_{max}	17-19 hours	CYP3A4	No
Suvorexant	82%	Food delays T_{max}	15 hours	CYP3A4 (primary); CYP2C19 (minor)	No
Melatonin agonist					
Ramelteon	1.8%	Food delays T_{max}	1-2.6 hours	CYP1A2, CYP2C19, CYP3A4	No
Azapirone					
Buspirone	3.9%	Food increases bioavailability by decreasing first-pass metabolism	2.5 hours	CYP3A4	Yes

Note. CYP = cytochrome P450; T_{max} = time to peak drug concentration.

[a] Oxazepam and temazepam are active metabolites of diazepam.

Opioid and related compounds

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Buprenorphine	45% (sublingual)	None	24-60 hours	CYP3A4	No
Naltrexone	5%-40%	None	4-10 hours	Dihydrodiol dehydrogenase metabolizes naltrexone to its primary metabolite, 6b-naltrexol	No
Samidorphan	69% (oral); 71%	None	7-9 hou	CYP3A4	No

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
	(sublingual)		rs		

Procognitive drugs

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Amantadine	66%-100%	None	17 hours	No appreciable metabolism	Yes, if CrCl < 50 mL/minute
Donepezil	100%	None	70 hours	CYP3A4	No
Galantamine	90%-100%	Food decreases C_{max} by 25% and delays T_{max} by 1.5 hours	7-8 hours	CYP2D6, CYP3A4	Yes, if CrCl < 60 mL/minute
Memantine	100%	None	60-100 hours	*N*-glucuronidation	Yes, if CrCl < 30 mL/minute
Rivastigmine	40%	Food delays absorption and lowers C_{max} and AUC by 30%	1.5 hours	Metabolized primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite NAP226-90	No data

Note. AUC = area under the curve; C_{max} = maximum concentration; CrCl = creatinine clearance; CYP = cytochrome P450; T_{max} = time to peak drug concentration.

Vesicular monoamine transporter 2 (VMAT2) inhibitors

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?

Agent	Oral bioavailability	Effect of food with oral administration	Half-life ($t_{1/2}$)	Primary metabolic pathway	Renal dosing required?
Deutetrabenazine	80%	Food increases C_{max} by about 50%	9-10 hours	CYP2D6	No
Valbenazine	49%	Food decreases AUC by about 47%	15-22 hours	CYP3A4/5; [+]-a-dihydrotetrabenazine metabolite partly metabolized by CYP2D6	No

Note. AUC = area under the curve; C_{max} = maximum concentration; CYP = cytochrome P450.

CHAPTER 7

Neuroimaging and Psychiatry

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Researchers utilizing noninvasive in vivo human brain imaging techniques have long searched for objective biological markers for psychiatric disorders, the discovery of which would advance psychiatry from an era of subjective descriptive classification to one of quantitative brain-based measurements (Abi-Dargham and Horga 2016). Yet, objective neuroimaging markers in psychiatry have been elusive; therefore, the impact of neuroimaging-based approaches on pragmatic clinical decision-making in psychiatry is so far extremely limited. Moreover, several methodological issues in the neuroimaging literature have been highlighted in recent years, including small sample sizes and the resulting power failures leading to a "replication crisis" (Button *et al.* 2013; Kharabian Masouleh *et al.* 2019; Poldrack *et al.* 2017; Szucs and Ioannidis 2017), as well as a dependency on analysis pipelines (Botvinik-Nezer *et al.* 2020) and modest test-retest reliability (Esteban *et al.* 2020), which further hinder the potential application of neuroimaging in clinical psychiatry.

The crux of the problem is that many of our findings with neuroimaging approaches are still based on relatively small datasets. In a previous meta-analysis (Feng *et al.* 2022), we showed that effect sizes are vastly overestimated with these small sample sizes and that the results typically do not stabilize until one has reached several hundred participants. Larger population-representative sample studies support the notion that variability in structural and functional brain imaging accounts for only a small percentage of explained variance when a variety of clinical phenotypes are considered. For instance, a 2016 analysis of UK Biobank data revealed that the fusiform gyrus and amygdala activation related to a face processing task accounted for a maximum of 1.8% of the variance of 1,100 non-neuroimaging variables (Miller *et al.* 2016). These findings are in line with emerging results from the ABCD Study, such as the association between screen media behavior and structural MRI characteristics (Paulus *et al.* 2019). Together, these findings suggest that individual processing differences as measured by neuroimaging techniques (or other methods) could account for little symptomatic or behavioral variance (Paulus and Thompson 2019).

In this chapter we review the most robust findings in structural and functional neuroimaging as they relate to psychiatric disorders. Following the available literature, the bulk of information will refer to MRI methods, with a briefer mention of PET, a technique that is older, but less commonly used, than MRI. The strategy taken here is to use only meta-analyses of neuroimaging findings to highlight which neural substrates are affected across disorders and within a particular disorder, and which brain areas change as a function of treatment. Although some have criticized the excessive use of meta-analyses (Ioannidis 2010; Ioannidis *et al.* 2015), these approaches still provide qualitatively better evidence than do small, single-site neuroimaging experiments. However, this is changing with the advent of epidemiologically based neuroimaging like ABCD (Volkow *et al.* 2018) or the UK Biobank (Miller *et al.* 2016), although the diagnostic assessments of these studies rarely are as intense and detailed as they are in many of the smaller clinical studies.

There are a couple of caveats that one needs to keep in mind when examining the presented evidence. First, most of the meta-analyses are based on case-control, cross-sectional studies, which have a limited ability to identify causal factors underlying the observed clinical presentation. Therefore, most--if not all--of these studies are associative in nature and will suffer significant limitations in determining whether the neuroimaging findings are causes, consequences, or non-disease-relevant associated observations. Second, meta-analyses necessarily must pool across different approaches that range from acquisition of the imaging data to analyses arriving at the summary statistics. Therefore, heterogeneity is baked into the results of the meta-analysis from the start. Third, meta-analyses cannot fundamentally overcome some of the imaging limitations. For example, although the statistical characteristics of structural neuroimaging such as reliability and external validity have been examined in detail and were found to be at a level similar to what is being observed for standard clinical instruments, the reliability and external validity of functional neuroimaging data are much more debated. Fourth, it is increasingly clear that our diagnostic categories do not simply map onto differential structural or functional changes in the brain. The Research Domain Criteria (RDoC) approach (Insel *et al.* 2010) was an initial attempt to separate psychiatric disorders into different transdiagnostic disease processes. This approach has had some success but has also faced significant challenges (Bzdok and Meyer-Lindenberg 2018; Conway *et al.* 2019; Hennessey *et al.* 2018). For example, diagnostic categories such as major depressive disorder not only are characterized by dysfunctional processes (e.g., reduced ability to process rewarding events) but also exhibit an episodic dysfunction of positive and negative valence processing (i.e., during periods of depression, individuals have difficulty processing "good" or "bad" events appropriately). This overview of neuroimaging and psychiatry will take a current, state-of-the-art critical view of what has been accomplished based on both structural and functional MRI, and, to a lesser extent, PET approaches. The goal is to provide insights into the emerging patterns of brain-associated changes in psychiatric disorders as well as specific changes that may help to identify novel targeted interventions based on neuromodulatory tools.

Process-Specific Approaches

The basic experimental approach of neuroimaging research is to define a particular process (e.g., the processing of emotions as expressed in human faces), examine the change in brain signaling during this process, and--using thoughtful experimental manipulation or group comparisons--delineate a model that describes how the brain implements this particular process. However, defining a "process" is a highly heuristic endeavor, and we are far from understanding the fundamental "atomic" processes that make up our cognitive and emotional experiences. Functional neuroimaging measures mass action of neural tissue when individuals process information originating from the outside world or from the inside of the body. The assumption is that greater or lesser "activation" is due to greater or lesser engagement of mass action during a specific process. Thus, greater or lesser engagement could be due to a) less-or more-efficient processing of information (i.e., neural activation is needed to accomplish a process); b) greater or lesser involvement due to "deeper" or "more extensive" or "shallower" or "more restricted" processing of the information; or c) engagement of different brain systems in processing the information, which results in greater or lesser activation of the neural tissue under study. Although intuitive, much of the relationship between neural processing intensity and intensity of the affective or cognitive process is still unclear (Lebreton *et al.* 2019).

In this section, we review a few processes that are critically important for different psychiatric disorders and for which meta-analyses have provided robust evidence for their underlying neural substrates. It is arguable that each of these processes could be split further into smaller components, which may provide another way of identifying more targeted differences in individuals with psychiatric disorders.

One of the most important processes for psychiatric disorders is our ability to process emotions. Meta-analyses show that there is currently no evidence that emotion processing in the brain falls in line with what has been called the *bivalent hypothesis*, which proposes that different brain systems compute positive or negative emotions, or the *bipolarity hypothesis*, which proposes that brain systems increase or decrease with a particular positive or negative emotion, respectively. Instead, it appears that brain activations fall more in line with the *affective workspace* hypothesis, which suggests that positive and negative affect are supported by a flexible set of valence-general regions (Lindquist *et al.* 2016). Many experimental approaches probing affect involve processing of facial expressions, which is supported by a network of structures, including the visual, limbic, and temporoparietal and prefrontal areas; the putamen; the cerebellum; and, most importantly, the amygdala and insula (Fusar-Poli *et al.* 2009). As will become evident once transdiagnostic or diagnostic groups are considered, it should not be surprising that the function of many of these brain areas is significantly affected in psychiatric disorders.

Anticipation is an important component of emotion processing and is supported by the insula, cingulate, amygdala, thalamus, and caudate (Andrzejewski *et al.* 2019), areas that are sensitively affected in mood and anxiety disorders. (Figure 7-1 summarizes the brain areas involved in processing anticipatory emotional information.) In comparison, it does not appear that emotion-based approach or avoidance behavior can be related to a delineated set of neural substrates; however, there appears to be a shift from forebrain to midbrain as threat-related stimuli become more imminent (Patrick *et al.* 2019). In the context of processing positive or negative events, social reward plays an important role in most psychiatric conditions and involves a number of brain regions, most notably the ventral striatum. Not surprisingly, some diagnostic groups show moderately attenuated processing of social rewards, whereas others (e.g., bipolar disorders, eating disorders, sexual disorders) exhibit increased activation to social rewards (Aldridge-Waddon *et al.* 2020). Fear conditioning and extinction have been used to explain anxiety-related disorders in terms of increased conditioning, attenuated extinction, or overgeneralization of conditioned stimuli. Several meta-analyses have shown that a network of brain regions, including in particular the anterior insular cortex and anterior cingulate, processes the conditioning and extinction processes (Fullana *et al.* 2016). In comparison, a network of cingulo-opercular, frontoparietal, striatal-thalamic, and midbrain regions is involved in positive generalization, whereas ventromedial prefrontal cortex, hippocampus, middle temporal gyrus, and angular gyrus process negative generalization (Webler *et al.* 2021). Taken together, a network of brain structures, most notably anterior insula and anterior cingulate, is commonly found in different components of emotion processing that are relevant for psychiatric disorders.

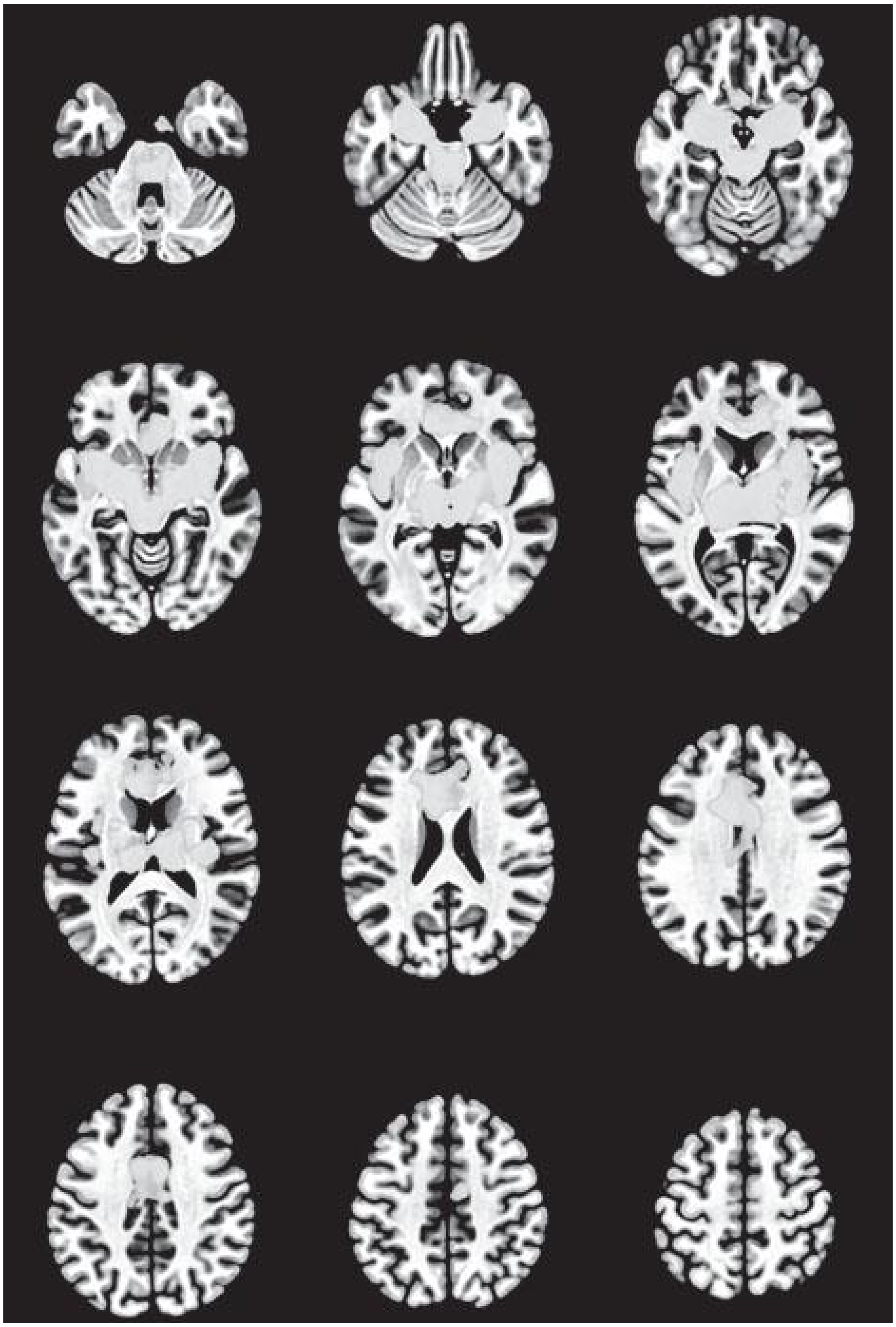

FIGURE 7-1. Axial slices of prospective meta-analysis using NeuroQuery,[a] indicating the predicted activations to the keywords "anticipation, emotion, anxiety, depression."

See Plate 26 to view this figure in color.

The color codes represent thresholded (at 3.0) *z* values. As indicated in the text, the following brain structures are predicted to be significantly activated: midline cortical structures, insula, amygdala, and thalamus.

[a] NeuroQuery (neuroquery.org; Dockes *et al.* 2020).

On the other hand, alterations in cognitive processes, which are frequently associated with psychiatric disorders such as schizophrenia, involve a different set of brain structures, notably the left superior temporal gyrus and left posterior middle temporal gyrus (Wensing *et al.* 2017). In comparison, perseverative cognition such as worrying or rumination involves the left middle frontal gyrus, left inferior frontal gyrus, and left anterior insula (Weber-Goericke and Muehlhan 2019). Others have reported that in individuals with psychiatric disorders, ruminative cognitions are also associated with activation in the medial frontal gyrus, cingulate gyrus, insula, and posterior cingulate cortex (Makovac *et al.* 2020). Altered perceptions such as auditory or visual hallucinations are associated with activation in the bilateral inferior frontal gyrus, bilateral postcentral gyrus, and left parietal operculum, whereas the propensity to experience such perceptual abnormalities occurs in individuals with altered processing within the left superior temporal gyrus, left middle temporal gyrus, anterior cingulate cortex, and left premotor cortex (Kuhn and Gallinat 2012). These findings point toward the notion that altered cognitive and perceptual symptoms are processed by systems typically found to be important for nonclinical populations. Therefore, one might conclude that clinically symptomatic cognition and perception are an excessive extension of normally occurring processes. Figure 7-2 summarizes the brain areas involved in cognitive and perceptual processing.

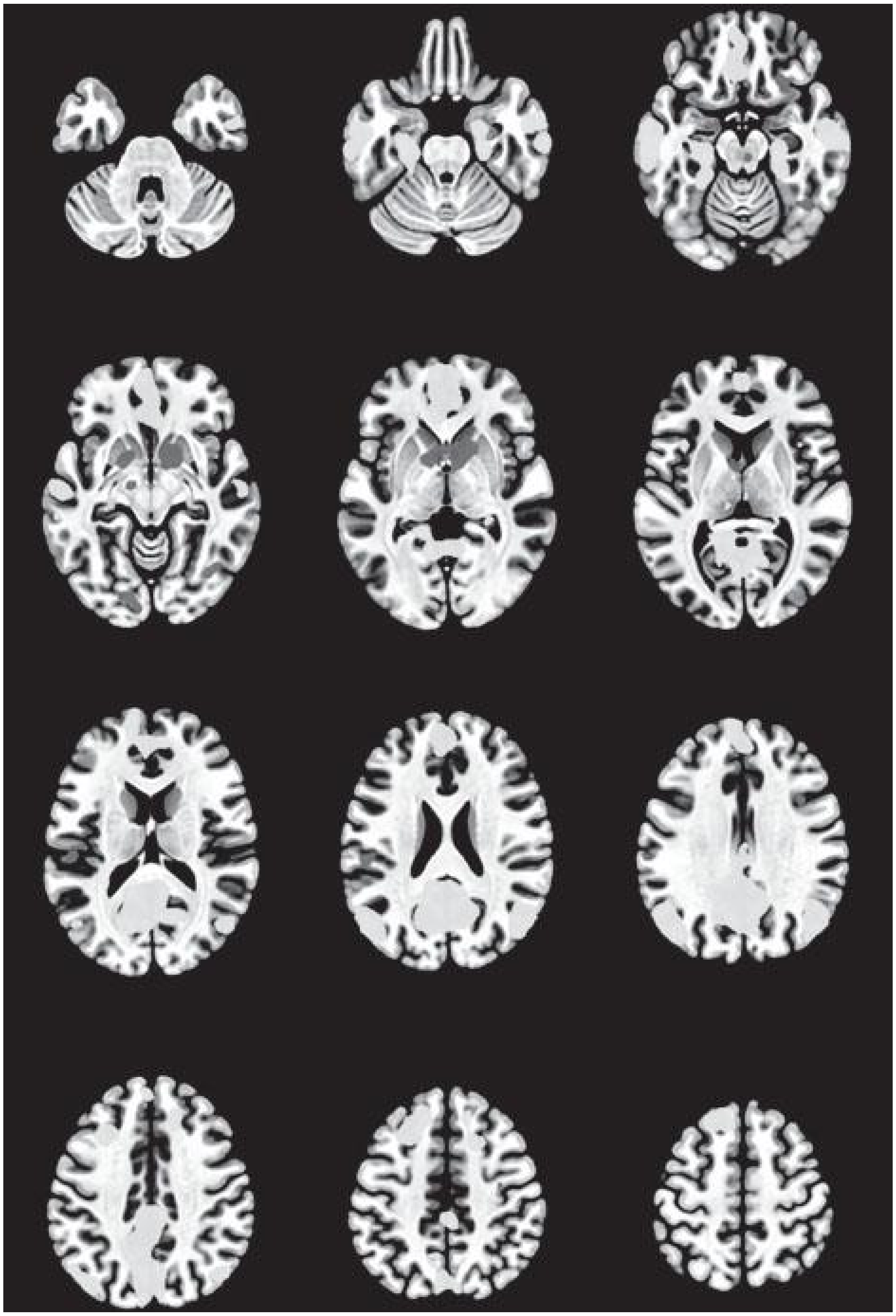

FIGURE 7-2. Axial slices of prospective meta-analysis using NeuroQuery,[a] indicating the predicted activations to the keywords "formal thought disorder, schizophrenia."

See Plate 27 to view this figure in color.

The color codes represent thresholded (at 3.0) *z* values. As indicated in the text, the following brain structures are predicted to be significantly activated: posterior cingulate, midline cortical structures, precuneus, superior temporal gyrus, and middle frontal gyrus.

[a] NeuroQuery (neuroquery.org; Dockes *et al.* 2020).

Transdiagnostic Approaches

Transdiagnostic approaches have gained a lot more attention since the National Institute of Mental Health began the RDoC project in 2009 to develop a research classification system for mental disorders based on neurobiology and observable behavior (Cuthbert and Insel 2013). The RDoC initiative highlights the need to 1) determine the relationships among different units of analysis (i.e., genes, molecules, cells, circuits, physiology, behavior, self-report, and paradigms) and 2) transcend traditional diagnostic groups to adequately capture the variation of domains in clinical populations that can be mapped across units of analysis. This approach is--to some degree--supported by the finding that brain structural abnormalities in major depressive disorder, bipolar disorder, schizophrenia, and OCD are highly correlated (Radonjic *et al.* 2021), which can be captured by one shared latent underlying factor that can explain as much as 80% the brain structural variance of each disorder (Opel *et al.* 2020). Specifically, gray matter loss across diagnoses can be seen in the dorsal anterior cingulate, right insula, and left insula and is associated with poorer cognitive functioning (Goodkind *et al.* 2015). Whereas altered cognitive control processing across disorders is evident in the left prefrontal cortex as well as the anterior insula, dorsal cingulate cortex, right ventrolateral prefrontal cortex, right intraparietal sulcus, and midcingulate/presupplementary motor area (McTeague *et al.* 2017), affective processing abnormalities have been associated with altered activation in the amygdala, the hippocampal or parahippocampal gyri, the dorsomedial or pulvinar nuclei of the thalamus, and the fusiform gyri, as well as the medial and lateral dorsal and ventral prefrontal regions

(McTeague *et al.* 2020). Recently, transdiagnostic interoceptive dysfunctional processing has been related to altered insula activation (Nord *et al.* 2021). In comparison, across task-based functional MRI (fMRI) the most pronounced transdiagnostic differences are found in the amygdala and caudate nucleus, hippocampus, putamen, and nucleus accumbens (Sprooten *et al.* 2017). In summary, both structural and functional neuroimaging studies support the idea that general and task-specific processing dysfunctions occur transdiagnostically in brain areas that have been previously identified as critical for integrative processing. However, much work is still necessary to link such transdiagnostic brain structure and function abnormalities to clinical parameters such as risk for and severity and consequences of the disease process.

Diagnosis-Specific Imaging Findings

Schizophrenia

Most neuroimaging meta-analyses have been conducted for schizophrenia, which has resulted in a solid body of evidence of both structural and functional alterations that have been associated with the disorder in general and with symptoms or outcomes specifically. Structural MRI meta-analyses show that intracranial volume and total brain volume are decreased by 2% in medicated schizophrenia patients and that the decrease is even more pronounced in medication-naive individuals (Haijma *et al.* 2013). Medicated individuals show decreased volumes of the left lateral temporal cortex, left inferior frontal gyrus, superior frontal gyrus extending to the left middle frontal gyrus, and right rectal gyrus; in comparison, relative volumetric increases are found in the left dorsal anterior cingulate cortex, left ventral anterior cingulate cortex, and right putamen (Torres *et al.* 2013). Moreover, individuals with schizophrenia have significantly smaller hippocampi (Haukvik *et al.* 2018). Although there has been vigorous debate about the heterogeneity of the disorder, analysis of the variability among imaging findings did not reveal greater imaging variability, especially for some of the pronounced findings such as ventricular volume increases (Kuo and Pogue-Geile 2019). Multimodal imaging analysis provides evidence for considerable overlap between anatomic and functional changes in brain areas including frontotemporal regions, bilateral medial posterior cingulate/paracingulate gyrus, bilateral insula, basal ganglia, and left cerebellum (Gao *et al.* 2018). Beyond the disorder stage, ultra-high-risk individuals exhibit greater gray matter volumes in the bilateral cingulate, right fusiform gyrus, left superior temporal gyrus, and right thalamus but decreased volumes in the right gyrus rectus, right superior frontal gyrus, and left superior frontal gyrus (Ding *et al.* 2019). On the other hand, the schizophrenia deficit state has been associated with a profound reduction in gray and white matter volume (Chee *et al.* 2020). Taken together, structural imaging meta-analyses find extensive cortical volume reductions and ventricular size increases, with some of these changes predating illness onset, and others (more widespread changes) being associated with the deficit stage of the disorder.

Functional neuroimaging meta-analyses have revealed substantial deficits in processing as well as related attenuated brain activation during *cognitive control* in the left dorsolateral prefrontal cortex, rostral/dorsal anterior cingulate cortex, left thalamus, and inferior/posterior cortical areas (Minzenberg *et al.* 2009); *working memory* in the bilateral dorsolateral prefrontal cortex and posterior parietal cortex as well as the anterior insula, anterior cingulate cortex, and supplementary motor area (Wu and Jiang 2020); *auditory processing* in the left primary auditory cortex and right rostral prefrontal cortex (Kompus *et al.* 2011); *facial processing* in the bilateral amygdala, parahippocampal gyrus and fusiform gyrus, right superior frontal gyrus, and lentiform nucleus (Li *et al.* 2010) as well as the insula (Dong *et al.* 2018); *emotion processing* in the bilateral amygdala, visual processing areas, anterior cingulate cortex, dorsolateral frontal cortex, medial frontal cortex, and subcortical structures (Anticevic *et al.* 2012; Taylor *et al.* 2012); *neutral affective material processing* in the left and right amygdala and parahippocampus and the left putamen, hippocampus, and insula (Dugre *et al.* 2019); and across task domains in subcortical basal ganglia (Bernard *et al.* 2017). Beyond task-based and location-specific changes, it appears that functional activation characteristics are also changed in terms of underlying network structure

(Crossley *et al.* 2016), particularly with regard to local connectedness (Kambeitz *et al.* 2016). Finally, it appears that cognitive retraining does improve activation patterns in prefrontal areas, but its effects are modest and variable (Mothersill and Donohoe 2019). Thus, like the structural findings in schizophrenia, functional imaging studies show a widespread attenuation that involves process-specific areas but also includes task-independent structures such as the prefrontal cortex, subcortical structures, and limbic areas.

Bipolar Disorder

Early findings of structural abnormalities (Strakowski *et al.* 1999) were subsequently replicated in meta-analyses finding robust structural differences between individuals with bipolar disorder and comparison subjects; these differences involve areas that are important for regulation of emotions, such as limbic areas (Houenou *et al.* 2011), but also the right ventral prefrontal cortex, insula, temporal cortex, and claustrum (Selvaraj *et al.* 2012). Relative to nonpsychotic patients with bipolar disorder, psychotic bipolar patients show greater reductions in the prefrontal, temporal, and cingulate cortices as well as in the precentral gyrus and the insula (Wang *et al.* 2018).

Interestingly, two meta-analyses found evidence for lithium treatment-modulated structural brain differences in the hippocampus (Hajek *et al.* 2012) and global brain volume (Sun *et al.* 2018). The predominant functional changes observed in patients with bipolar disorder involve brain regions that are important for emotion processing, with increased activation in ventral limbic brain regions (Houenou *et al.* 2011). Moreover, during emotion processing, youths with bipolar disorder show greater convergence of hyperactivation in the inferior frontal gyrus and precuneus than do adults with bipolar disorder (Wegbreit *et al.* 2014). Extending these findings to the relatives of individuals with bipolar disorder, these individuals show greater activation in frontostriatal regions but reduced activation in the parietal cortex during cognition, as well as increased activation in the amygdala during emotional processing and in the orbitofrontal cortex during reward, relative to healthy control subjects (Cattarinussi *et al.* 2019). These findings are consistent with the idea of a preexisting imbalance of cognitive/affective processing, which is further supported by similar changes in individuals with first-episode mania (Keramatian *et al.* 2021). In summary, both structural and functional neuroimaging findings in bipolar disorder implicate impaired emotion processing, which may exist prior to illness onset and occurs subtly in family relatives, but which can also be affected by treatment.

Depression

Structural neuroimaging meta-analyses have shown that in comparison with healthy control subjects, individuals with depression have lateral ventricle enlargement; larger cerebrospinal fluid volume; and smaller volumes of the basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex, and gyrus rectus (Kempton *et al.* 2011). Others reported thinner cortical gray matter in the orbitofrontal cortex, anterior and posterior cingulate, insula, and temporal lobes in depressed patients compared with healthy controls (Schmaal *et al.* 2017). A relatively consistent feature has been bilateral hippocampal atrophy (Santos *et al.* 2018), which was also observed during symptom-free intervals (Kempton *et al.* 2011). In comparison, functional neuroimaging findings have been more variable. Initially, there was relatively little evidence for a common task-based fMRI network dysfunction (Gray *et al.* 2020). However, other analyses yielded hypoactive clusters in the anterior insular and rostral anterior cingulate cortex (Sacher *et al.* 2012) as well as the subgenual anterior cingulate cortex (Diener *et al.* 2012). Two specific processing dysfunctions can be observed in participants with depression relative to healthy comparison subjects. First, there is increased activation associated with social cognitive processing in areas of the brain related to emotions, such as the limbic structures, but decreased activity in the frontal regions of the brain (Cusi *et al.* 2012). Second, there is increased brain activation associated with negative stimuli, with heightened responses in the amygdala, insula, and dorsal anterior cingulate cortex, but reduced activation in the dorsal striatum and dorsolateral prefrontal cortex (Hamilton *et al.* 2012). A distinguishing feature between individuals with and without depression is the level of activation in the lateral frontal areas of the brain, which appears to respond to therapeutic interventions (Graham *et al.* 2013). Resting state fMRI meta-analyses have found increases in intrinsic activity in the anterior cingulate cortex (Zhou *et al.* 2017), and these changes appear to be sufficiently strong to yield a relatively high separation of groups based on machine learning approaches (Kambeitz *et al.* 2017).

There is a paucity of meta-analyses of PET and SPECT studies in depression, and those that have been published have focused on three main themes: regional brain metabolism, serotonin neurotransmission, and neuroinflammation. The latter two areas of research cannot be addressed with MRI and therefore are of greater pathophysiological interest. One meta-analysis has examined serotonin$_{1A}$ receptor (5-HT$_{1A}$) alterations in depression (Wang *et al.* 2016). These authors concluded that a significant, albeit small, effect was the reduction of 5-HT$_{1A}$ receptors in middle temporal structures. An earlier study of 5-HT transporters (Gryglewski *et al.* 2014) found reductions in 5-HT transporter density in the midbrain and amygdala that were not detected in individual PET or SPECT studies; the decrease in 5-HT transporters in the amygdala was related to severity of depression. A review of in vivo molecular studies of serotonin neurotransmission in individuals with suicidal behavior offered inconsistent results (Desmyter *et al.* 2011). Finally, a recent meta-analysis of studies focusing on central inflammation, an important conceptual avenue for depression pathophysiology (Enache *et al.* 2019), showed that PET studies of translocator protein, a central inflammation marker, revealed significant abnormalities in the anterior cingulate and temporal cortices in major depressive disorder. In summary, although structural neuroimaging findings have been relatively solid, functional changes appear to be more variable, but the findings seem to converge on differences within the medial wall of the cortex, including the anterior cingulate, across different affective processes.

Anxiety

Although no meta-analyses of structural neuroimaging studies specifically focused on anxiety disorders have been conducted as of this writing, there is converging evidence from various functional neuroimaging meta-analyses of a consistent dysfunction of several core neural structures. In one of the earliest meta-analyses across task-related fMRI studies, anxiety disorders were found to be associated with hyperactivity in the amygdala, insula, anterior cingulate, and prefrontal cortex (Etkin and Wager 2007). Others observed that some of the same structures (Gentili *et al.* 2016) and those involved in facial processing, including the bilateral amygdala, globus pallidus, superior temporal sulcus, visual cortex, and prefrontal cortex, were altered in individuals with social anxiety disorder (Bruhl *et al.* 2014). A slightly different pattern can be found in OCD, with increased activation in the bilateral amygdala, right putamen, orbitofrontal cortex extending into the anterior cingulate and ventromedial prefrontal cortex, and middle temporal and left inferior occipital cortices during emotional processing (Thorsen *et al.* 2018). There does not seem to be a fundamentally different functional activation pattern whether the anxiety is experimentally induced in those without anxiety disorder or is observed as part of the illness (Chavanne and Robinson 2021). Although PTSD is technically no longer considered an anxiety disorder, meta-analyses of individuals with PTSD have revealed a similar pattern of functional abnormalities. Specifically, exaggerated activation to trauma stimuli was found in the midline retrosplenial cortex and precuneus, pregenual/anterior cingulate gyrus, and bilateral amygdala, while less activation was found in the bilateral temporal gyri and extrastriate area (Sartory *et al.* 2013). In addition, general hyperactivity during a functional task has been reported for the bilateral insula and cingulate cortex as well as for the parietal, frontal, and limbic areas (Boccia *et al.* 2016). Furthermore, structural neuroimaging

meta-analyses involving adults with PTSD have revealed reduced total corpus callosum areas, reduced total cerebral and intracranial volumes, and reduced total hippocampus, amygdala, and frontal lobe volumes (Milani *et al.* 2017), and similar reductions in these areas have been reported among pediatric patients with PTSD (Kribakaran *et al.* 2020). In summary, a core network of amygdala, insula, and midline prefrontal cortex has been found to differ both structurally (for PTSD) and functionally (for anxiety disorders) from the network in healthy comparison subjects.

Substance Use Disorders

Structural meta-analyses show that across all substances, convergent pathology was evident in the gray matter of the insula, anterior cingulate cortex, putamen, and thalamus, and in the white matter of the thalamic radiation and internal capsule bundle (Pando-Naude *et al.* 2021). Moreover, decreases in gray matter have also been reported in the bilateral prefrontal cortex, bilateral insula, bilateral rolandic operculum, left superior temporal gyrus, and right Heschl gyrus, while increases in gray matter have been found in the right lingual gyrus and right fusiform gyrus (Zhang *et al.* 2021). So far, however, studies in at-risk individuals have not been able to find consistent structural abnormalities (Tervo-Clemmens *et al.* 2020). A similar set of structural abnormalities have been implicated in alcohol use disorder, including reduced gray matter in the corticostriatal-limbic networks (Li *et al.* 2021), especially the bilateral insula, superior temporal gyrus, striatum, dorsal lateral prefrontal cortex, precentral gyrus, anterior cingulate cortex, left thalamus, and right hippocampus (Yang *et al.* 2016). Not surprisingly, alcohol cue-induced enhanced functional activation has been reported for limbic and prefrontal regions, including the ventral striatum, anterior cingulate, and ventromedial prefrontal cortex, as well as the posterior cingulate, precuneus, and superior temporal gyrus (Schacht *et al.* 2013). In comparison with healthy control subjects, individuals with substance or alcohol use disorders show core structural and functional abnormalities in brain regions involved in processing the importance and value of the substance consumed, such as the insula, cingulate, and ventromedial prefrontal cortex. Similar abnormalities are also observed in subcortical structures, such as the striatum.

Neuroimaging Effects of Treatment

Several meta-analyses have been conducted to examine the effects of interventions to determine which neural substrates are affected and what patterns of activity might predict a positive response to treatment, and to identify possible targets for future neuromodulatory treatments. Task-based functional neuroimaging studies show that activations in the dorsomedial prefrontal cortex and in the posterior cingulate gyrus/precuneus change as a function of psychotherapy (Messina *et al.* 2013). In a meta-analyses of changes in brain activity accompanying psychological therapy based on both resting-state and task-based studies, there were decreases in activation in the anterior cingulate/paracingulate gyrus, inferior frontal gyrus, and insula after therapy, with changes in activation in the cuneus being predictive of subsequent symptom change (Marwood *et al.* 2018). Improved emotion regulation after psychotherapy is associated with activation in the dorsomedial prefrontal cortex and posterior cingulate gyrus/precuneus (Messina *et al.* 2013). In social anxiety disorder, activation in both the frontal and parietal cortical areas and the insula and cingulate cortex change as a function of either behavioral or pharmacological treatment (Li *et al.* 2016). Some have reported that perigenual anterior cingulate cortex activation was most robustly associated with repetitive transcranial magnetic stimulation (rTMS) treatment (Long *et al.* 2020). In a meta-analysis that included results from 20 functional imaging studies and 9 structural neuroimaging studies, Fu *et al.* (2013)) reported that increased baseline activity in the anterior cingulate was associated with a higher likelihood of improvement, while increased baseline activation in the insula and striatum was linked to a poorer clinical response. Structural neuroimaging studies have shown that a decrease in right hippocampal volume is a significant predictor of poorer treatment response. In another meta-analysis of psychotherapy treatment studies focused on neuroimaging to measure changes in patients with major depressive disorder, Sankar *et al.* 2018) found increased activity in the left rostral anterior cingulate posttreatment in patients and decreased activity in healthy control subjects. On the other hand, in a meta-analysis examining changes in brain metabolism related to various treatments for major depressive disorder (e.g., selective serotonin reuptake inhibitors, electroconvulsive therapy, rTMS), Chau *et al.* 2017) failed to find a consistent pattern for these treatments' effects in reducing depression.

Taken together, these findings suggest that among the core neural substrates that change after treatment are those that have also been observed to transdiagnostically differ from those of healthy comparison subjects in task-based activation studies, including the anterior cingulate and the prefrontal and parietal cortices (Figure 7-3). These findings suggest that although certain brain structures show treatment-relevant plasticity, there is currently limited evidence for treatment-specific networks that could become targets of future interventions.

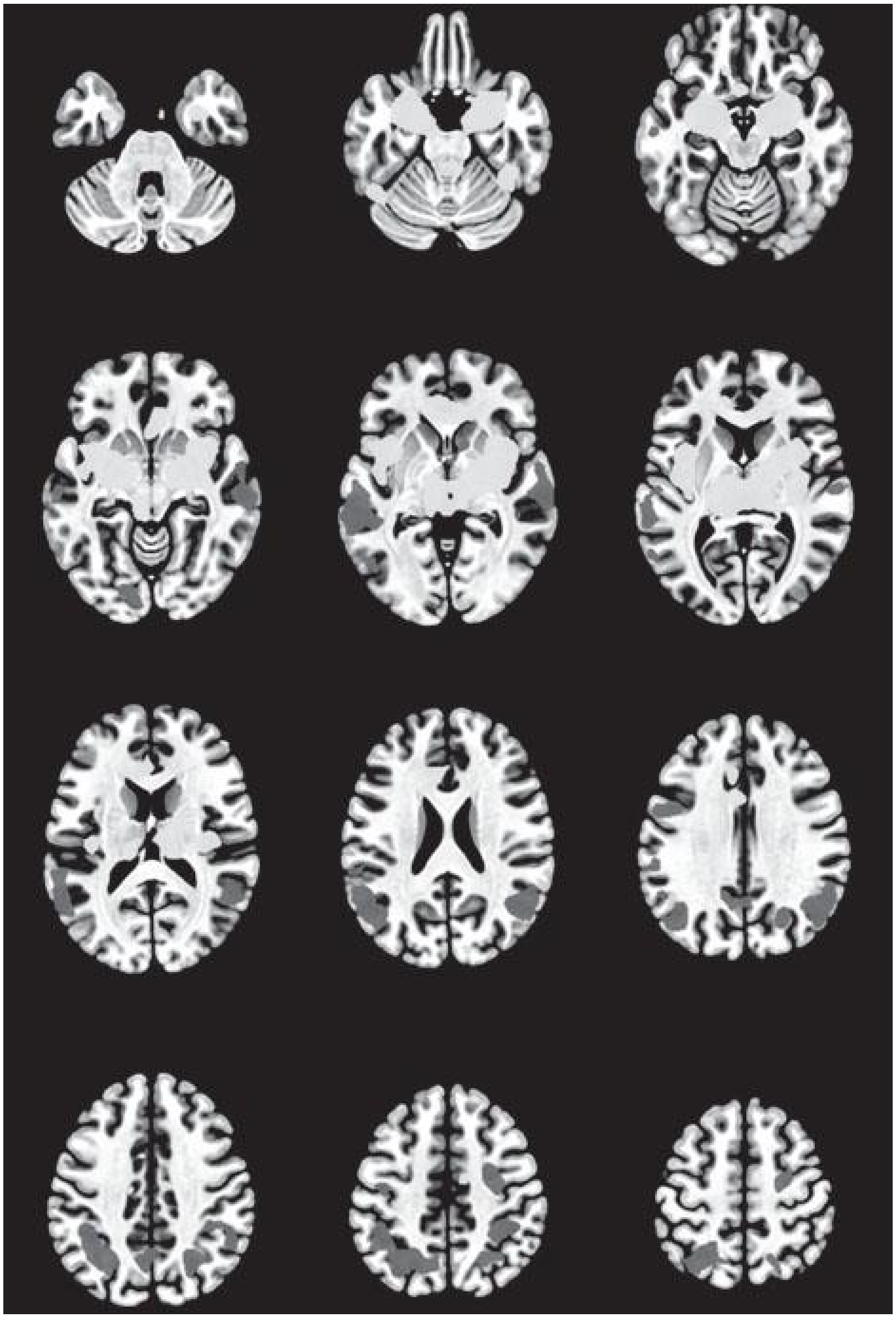

FIGURE 7-3. Axial slices of prospective meta-analysis using NeuroQuery,[a] indicating the predicted activations to the keywords "antidepressant, treatment, emotion."

See Plate 28 to view this figure in color.

The color codes represent thresholded (at 3.0) *z* values. As indicated in the text, the following brain structures are predicted to be significantly activated: amygdala, insula, anterior cingulate, posterior parietal, and thalamus.

[a] NeuroQuery (neuroquery.org; Dockes *et al.* 2020).

Conclusion and Future Directions

Several robust findings have emerged from the available meta-analyses of neuroimaging findings on neural substrates across psychiatric disorders. First, a core set of neural substrates show both structural and functional abnormalities across diagnoses and cognitive or affective processes. These include the cortical midline--most notably the different parts of the anterior cingulate--and the anterior insula. Functionally, these areas have been attributed to what has been termed the *salience network* (Seeley *et al.* 2007) but what others have termed *limbic motor cortex* and *limbic sensory cortex* (Craig 2003). These regions of the brain play a role in assigning importance or significance to the information being processed by the brain. They also aid in coordinating actions that are suitable responses to the importance of the information. It is notable that these areas are also among those that are sensitive to treatment effects, suggesting that these areas are at least partially responsible for the processes that underlie symptomatic phases of psychiatric disorders. The strongest empirical evidence for the role of the salience network is found in mood and anxiety disorders, which are characterized by an exaggerated activation across tasks during the symptomatic stages of these conditions. In addition, the structural and functional abnormalities observed in different disorders are consistent with the processes that are responsible for

the underlying symptoms. For example, content-related cognitive processing dysfunctions such as delusions, worrying, or repetitive negative thinking involve areas of the temporal cortex that are important for speech and memory. Similarly, auditory hallucinations are processed in the auditory cortex and show exaggerated activation patterns in individuals with schizophrenia. Lastly, enhanced cue reactivity, an important part of substance use abnormalities, is observed in subcortical areas that are critically important for reward-related processing. Taken together, these findings support the idea that processing abnormalities in psychiatric disorders reflect exaggerated or attenuated processes in brain structures that are important for these processes in healthy individuals. However, secondary brain areas often coactivate with these primary areas, suggesting that the symptomatic phases of a psychiatric illness reflect dysregulatory networks.

Further work is needed to better understand the nature of the brain processing dysfunctions that underlie psychiatric disorders. Areas that warrant focus include making better connections between structural MRI findings and the underlying anatomy and histology (Weinberger and Radulescu 2021), considering nonspecific imaging effects of pharmacological agents such as lithium (Lucini-Paioni *et al.* 2021), and better conceptualizing what resting state functional neuroimaging represents. In addition, the lack of meta-analytic findings from longitudinal imaging studies with psychiatric patients during different phases of their illness makes it very difficult to draw an accurate image of how brain function waxes and wanes during symptomatic and asymptomatic disease phases. In addition, we have only a rudimentary understanding of structural and functional brain plasticity in response to external influences such as stressors, changes in lifestyles, or relationships. Clinically, these factors are important determinants of change in psychiatric conditions, yet there is virtually no systems-level neuroscientific understanding of how these influences lead to exacerbations of the illness. Meta-analytic approaches can provide insights about "central tendencies"--that is, how an individual with a particular diagnosis might differ on average from a healthy comparison subject. However, very little can be gleaned about individual differences, subgroups, or illness heterogeneity. Although it has been difficult to establish disease heterogeneity, it seems clear that psychiatric diagnoses are not uniform entities and may consist of mixtures of processing dysfunctions that share a similar symptomatic appearance. This many-to-one mapping has been cited as one of the main challenges in better understanding the underlying neurobiological processes of psychiatric disorders (Paulus and Thompson 2019). Future analyses may need to use alternative approaches to begin to delineate robust subgroups of disorders with shared structural or functional neuroimaging characteristics. Much work will need to be done to obtain a more dynamic understanding of structural and functional neuroimaging characteristics of psychiatric disorders.

Several meta-analyses have shown that predicting group membership in a particular diagnostic category or predicting outcome using structural or functional neuroimaging data is possible in principle. Yet there is no current structural or functional neuroimaging procedure in place in a clinical setting to assist in determining a patient's diagnosis or prognosis. There are several reasons for this. First, despite these proof-of-principle findings, and even though meta-analyses are available, much uncertainty still exists as to how generalizable these findings are, how well they stack up once multiple disease groups are considered, and how robust these approaches can be in a clinical setting. Second, there is fundamentally a differential actionability problem. If a diagnosis were to be made using neuroimaging, what different actions would one take to optimize clinical outcomes? There are no studies that show convincingly that neuroimaging-assisted diagnosis or prognosis results in measurably better outcomes for patients. These studies are very difficult to do because they would need to be conducted in multiple sites, using a randomized controlled trial design, and to have prespecified action plans and outcomes. However, short of such evidence, the ultimate utility of neuroimaging for clinicians is an aspirational goal.

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CHAPTER 8

Personalized Medicine in Psychiatry

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The Global Burden and the Unmet Needs of Psychiatric Disorders

The 2019 Global Burden of Diseases, Injuries, and Risk Factors Study estimated that mental and addictive disorders, mainly depressive disorders, are a primary cause of nonfatal burden (Abbafati *et al.* 2020) and account for 19% of all years lived with disability (Rehm and Shield 2019).

Despite a vast array of pharmacological and nonpharmacological therapeutic options, the clinical and functional outcomes of mental disorders remain unsatisfactory (Caldirola and Perna 2019). This is partly because reliable methods for identifying the most effective treatment for each patient remain elusive.

Until the twentieth century, medical practice was based on careful observation and clinical judgment. Thereafter, clinical practice guidelines, founded on the principles of evidence-based medicine, emerged, with recommended clinical and therapeutic choices based on a systematic assessment of the available evidence supported by committees of experts

(Lee *et al.* 2020). Although these guidelines represented an improvement with respect to subjective opinions, treatment recommendations were founded on the average response of the clinical population participating in randomized clinical trials without relating the response to specific individual characteristics. Moreover, it was found that evidence-based practices take 17 years, on average, to be incorporated into the health care routine, and only about half of them are widely used in the clinical setting (Bauer and Kirchner 2020). Clinician cognitive factors, such as confirmation bias (i.e., the tendency to search for, interpret, and recall information in

a way that confirms one's prior beliefs), are thought to contribute to the delay in implementation of clinical practice guidelines (Perna and Nemeroff 2022).

Personalized Medicine: A New Approach

Recently, attention has shifted toward the personalized or precision medicine approach that aims to tailor the best diagnostic and treatment decisions for each patient by integrating clinical, biological, and environmental factors (Perna and Nemeroff 2017). Personalized medicine aims to predict an individual's susceptibility to disease, achieve an accurate diagnosis, and select the best therapeutic option for each person to increase the likelihood of effective response and reduce the occurrence of adverse effects (Sugeir and Naylor 2018).

Personalized predictive models of diagnosis and outcomes are based on the collection of very-large-scale data (so-called big data) that are analyzed using advanced computational tool kits capable of making a prediction from such information (e.g., machine learning methods) (Sugeir and Naylor 2018).

Before being considered and applied in the field of psychiatry, personalized medicine yielded significant breakthroughs in oncology in a study in which the administration of the monoclonal antibody trastuzumab only to the subgroup of women who were HER2-positive was an example of a treatment "personalized" to patients who would benefit the most (Hingorani *et al.* 2013).

The National Research Council found the original term *personalized medicine* to be equivocal, as it implies that unique treatments can be designed for each individual; thus, they suggested that it be changed to *precision medicine* (National Research Council 2011). Although several authors use the terms *precision medicine* and *personalized medicine* synonymously, a recent literature review indicated that *personalized psychiatry* has been more often used in studies addressing mental disorders over a broad range of topics (clinical, biological, and therapeutic) (Perna *et al.* 2020c). Alternatively, the term *precision psychiatry* has been mainly used in investigations of the purely biological context of mental diseases.

Current Difficulties in Personalized Medicine in Psychiatry

In contrast to many medical illnesses, psychiatric disorders are inherently complex because they are related to brain dysfunctions at multiple levels (from neuron to brain connectivity) and amply intertwined with social, cultural, and experiential factors. This peculiarity makes the development of *personalized medicine in psychiatry* (PMIP) even slower and more challenging than in other medical fields.

The Challenge of Psychiatric Disorder Diagnosis

The currently available diagnostic tools DSM-5-TR (American Psychiatric Association 2022) and ICD-11 (World Health Organization 2022) fail to reflect the actual biological processes believed to underlie the identified disorders because they are mainly based on observable behaviors as well as self-reported emotions and thoughts. Despite this limitation, DSM-5-TR and ICD-11 organize the clinical observations in categorically distinct psychopathological entities constituting one of the cornerstones of therapeutic decisions in clinical practice. However, clinical and research evidence has demonstrated that the categorical approach fails to fully express the complexity of mental illness, which often occurs as combinations of several dimensional psychological alterations are sometimes shared by different disorders (Craddock and Owen 2005).

These drawbacks led to the development of the so-called dimensional approach, which defines psychiatric disturbances using a set of psychopathological dimensions encompassing a wide range of severity, from normality to the full expression of the dimension (Krueger and Bezdjian 2009). The potential clinical advantage of replacing the current categorical diagnostic system with a dimensional classification system has long been debated (Krueger and Bezdjian 2009). However, the dimensional scores used to directly make diagnoses need to overcome several limitations associated with the currently available dimensional measures to create specific patterns of independent and diagnostically relevant dimensional scores.

An innovative approach that is based on dimensions rather than categories is the Research Domain Criteria (RDoC) initiative (Insel *et al.* 2010), a classification system based on "dimensions of observable behavior and neurobiological measures" (Cuthbert 2015). The RDoC starts from the basic dimensions of behavior and cognitive/affective processing based on the biological systems and then considers psychopathology as a varying degree of abnormality in these systems, incorporating information from molecular factors to social determinants (Carcone and Ruocco 2017). It is noteworthy that the RDoC framework is a work in progress; thus, it consists of an initial panel of hypotheses that need to be tested and possibly reformulated based on the growth of our understanding. In spite of considerable investment in the RDoC initiative by the National Institute of Mental Health, the framework has fundamentally failed, with none of the funded research producing advances in either diagnosis or treatment.

Finding Biomarkers

The complexity of the diagnostic processes used for psychiatric disturbances makes it difficult to find a biomarker, which is described as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions" (FDA-NIH Biomarker Working Group 2021, p. 45).

In psychiatric disorders, the biological systems that have been the focus of most investigations are the inflammatory, neurotransmitter, neuroendocrine, neurotrophic, and metabolic systems. In the so-called omics approach, each dysregulated system can be evaluated at different biological levels, from genomics and epigenomics through transcriptomics and proteomics to metabolomics, which are collectively referred to as "multi-omics" (Olivier *et al.* 2019).

In PMIP, the information obtained from the different omics platforms is integrated with clinical data to predict forthcoming disease, diagnostic precision, and targeted prescription of the existing drugs. Omics technologies (i.e., next-generation sequencing for genomics and transcriptomics and mass spectrometry for proteomics and metabolomics) allow collection, in a single experiment, of a huge amount of data, such as billions of genome base pairs, the entire set of cell/tissue proteins, or low-molecular-weight metabolites (e.g., amino acids, lipids, and sugars) (Sethi and Brietzke 2015).

Information and Communications Technologies in Personalized Medicine in Psychiatry

Information and communications technologies allow for the discreet monitoring, in ecological settings, of behavioral, physiological, and cognitive/emotional factors that are collected using sensors, biosensors, and self-report instruments, respectively (Mohr *et al.* 2017).

Mobile Phones

Mobile phones are the most ubiquitous personal platform. Using embedded sensors and apps, such as accelerometers, geolocation, short message service, calls, and social network data, mobile phones collect behavioral information about people's habits, sleep patterns, and social interactions.

It has been demonstrated by Likamwa *et al.* (2013) that the number and length of communications, a person's locations, and app usage patterns are related to mood in nonclinical populations. In addition, mobile phones can be effectively used to deliver psychotherapeutic interventions (Mantani *et al.* 2018).

Wearable Devices

Wearable devices are sensor technologies designed to be worn on the wrist or clipped to the belt. They are generally used for specific purposes (health and fitness). These devices continuously track activities, such as the number of steps taken, miles traveled, and hours spent sleeping, including the length of REM and non-REM sleep, as well as heart rate and respiratory rate. Wearable devices record higher-quality data compared with smartphones; however, they were used by only about 20% of the U.S. population in 2018.

Electronic Medical Records

Electronic medical records (EMRs) contain a large amount of real-world patient information collected in standard clinical care. However, the clinical data included in the EMRs are usually not coded in formats that are suitable for statistical analysis (i.e., they are written in natural language that needs to be processed before analysis, and contain missing values and/or inhomogeneous set of data) (Perna *et al.* 2018). Favorably, previous literature demonstrated that the analytical techniques for extracting and coding relevant information from unstructured data (e.g., applying natural language processing tools to clinical notes) have high accuracy in terms of diagnostic classification of mood episodes (Castro *et al.* 2015). However, a recent systematic review on machine learning and natural language processing in mental health (Le Glaz *et al.* 2021) suggested that these techniques tend to confirm clinical hypotheses rather than aid in developing new information.

Technology-Based Ecological Momentary Assessment

Another promising contributor to PMIP is the potential of new digital technologies for psychiatry assessments and interventions. The technology-based *ecological momentary assessment* (EMA) is a strategy for assessing the psychopathological condition of a patient in naturalistic settings, allowing for a real-time collection of cognitive,

emotional, and behavioral data that can be stored and sent to clinicians and/or researchers. EMA-specific items, filled in several times a day, prompted by a scheduled signal from the device or around stressful events, include symptoms such as depressed mood, anxiety, and suicidal thoughts.

Compared with traditional clinical rating scales, EMA has many advantages. It allows for real time data collection (minimizing recall bias), analyzes changes that occur over time, and takes place in the individual's natural environment.

The apps for self-monitoring have prompted promising research on major depressive disorder (MDD) and suicidal behavior. EMA symptoms monitored in depressed patients were highly correlated with baseline Hamilton Rating Scale for Depression score (Hung *et al.* 2016) and significantly predicted response at week 6 after augmentation with quetiapine extended-release (XR) in MDD patients who had not responded to antidepressant treatment alone (Schaffer *et al.* 2013).

Correspondingly, real-time monitoring of suicidal thoughts via mobile EMA captures transient instances of suicidal ideation that may not be detected by traditional, retrospective, self-report measures. Detection of such transient instances helps identify subgroups of patients at risk for suicide who might otherwise have been missed (Gratch *et al.* 2021).

Monitoring of Physiological Parameters

The information collected by the EMA can be integrated with data obtained from wearable biosensors, which monitor physiological parameters throughout the day (Marzano *et al.* 2015), and smartphone-embedded sensors, which provide data on patients' behaviors and habits (Mohr *et al.* 2017). Thus, a panel of information that has the potential to revolutionize the traditional assessments of psychiatric illnesses is produced.

Computational Approach to the Complexity of Psychiatry

Recent developments in technology and data analysis methods may help overcome the complexity inherent in psychiatric practice. In machine learning, computer algorithms learn the general principles underlying a series of observations (training data) and successively apply such principles to never-before-seen cases without human guidance. The advantage of machine learning in PMIP is its ability to integrate large sets of variables and capture complex dependencies between variables.

Machine learning algorithms can be divided into three categories: supervised, unsupervised, and reinforcement learning models (Galatzer-Levy *et al.* 2018). *Supervised* models learn from a known, labeled training dataset to predict new output values. Its algorithms are designed to predict discrete (e.g., improvement or remission) or continuous (e.g., symptom severity) outcomes from clinical, genetic, or brain function data. *Unsupervised* models use unclassified/unlabeled training information and draw inferences from datasets to discover unknown statistical configurations (e.g., how variables cluster together or relate to one another) without reference to a specific and predefined outcome. *Reinforcement learning* models determine the optimal behavior to obtain the maximum reward through continuous interaction with the environment via a process similar to a trial-and-error search.

Personalized Prescribing in Psychiatry

PMIP aims to develop treatment according to the patient's specific characteristics by integrating information from clinical features, biomarkers, genetic factors, and environmental influences. In particular, recent advances in genetics technology have promised to transform the way drug treatments are prescribed to patients. The premise of genetically guided prescribing (pharmacogenetics) is to match the drug's pharmacological profile to the patient's genetic profile. Although the genetics-based prediction of the pharmacodynamic activity of psychiatric drugs is challenging because of the aforementioned diagnostic difficulties, the genetic factors that influence the pharmacokinetics of common psychiatric drugs are well known. Most psychotropic drugs are metabolized in the liver by enzymes of the cytochrome P450 (CYP) family, with their genetic variation significantly contributing to total drug exposure. Nevertheless, despite the enthusiasm due to the exponential reduction in genotyping costs (a polygene variant panel can now be performed for less than 100 U.S. dollars), routine use of pharmacogenetics prior to drug initiation is not yet supported by the empirical literature. Currently, psychiatric pharmacogenetics is considered the standard of care only for *HLA-B*15:02* genotyping before the initiation of carbamazepine in patients with Asian ancestry to predict the risk of Stevens-Johnson syndrome/toxic epidermal necrolysis emergence (Sung *et al.* 2020).

In the next section, we report on some of the main findings of the PMIP approach to treatment of psychiatric disorders.

Application of PMIP in Treatment of Psychiatric Disorders

Predicting Antidepressant Response in Major Depressive Disorder

MDD is a common, debilitating, and costly disease and is the subject of in-depth study using the PMIP approach. Despite the large number of antidepressant drugs (ADs) available, fewer than half of patients with MDD achieve remission of symptoms with their first prescribed antidepressant, and almost one-third fail to achieve remission even after four consecutive treatment trials (Warden *et al.* 2007), with a very negative impact on the severity and chronicity of the MDD course (Akechi *et al.* 2019).

PMIP, which develops therapeutic interventions according to the unique profile of each patient by integrating information from clinical features, biomarkers, and environmental factors, can be a crucial strategy for improving pharmacological responses in MDD.

Sociodemographic and Clinical Factors

Numerous studies have evaluated whether the variables that can be easily obtained in clinical practice through clinical interviews can be used to personalize the pharmacological treatment of MDD. The narrative review conducted by Perna and coworkers concluded that neither sociodemographic nor clinical variables, when considered independently, were reliable factors for the selection of a specific antidepressant class or compound in clinical practice (Perna *et al.* 2020a). Rather, the poor outcomes of the whole group of antidepressants were associated with low socioeconomic status, African genetic ancestry, overweight/obesity, very severe pretreatment depressive symptoms, depression with melancholic symptoms, and significant anxiety symptoms (Perna *et al.* 2020a).

Childhood maltreatment, which involves acts of commission or omission by parents or caregivers resulting in potential harm to the child's mental and physical health, is a further variable that can be obtained through clinical interviews. A large body of evidence (Lippard and Nemeroff 2020) clearly indicates that a history of childhood maltreatment is a predictor of poor outcome for all treatments for MDD (i.e., psychological therapy, antidepressants, or combined treatments). However, a recent systematic review that performed head-to-head comparisons of antidepressant treatments among MDD patients with or without a reported history of childhood maltreatment did not draw reliable conclusions on the possibility of childhood maltreatment assessment being used for selecting specific antidepressant classes or compounds because of the scarcity and heterogeneity of the included studies (Perna *et al.* 2021).

Increasing evidence has supported the relevance of inflammation in MDD, as suggested by increased peripheral levels of proinflammatory cytokines, chemokines, and C-reactive protein (Caldirola *et al.* 2021). In general, depressed patients with elevated inflammatory markers exhibit a poorer response to antidepressant treatment. A recent systematic review and meta-analysis (Liu *et al.* 2020) indicated that patients with MDD who exhibited a better response to antidepressant treatment had lower baseline interleukin-8 levels compared with nonresponders.

Pharmacogenetics

Single-nucleotide polymorphisms (SNPs) (i.e., single base-pair changes in the DNA sequence), which explain about 42% of the variance in antidepressant response (Tansey *et al.* 2013), could be utilized to personalize treatment choices. Several studies analyzed candidate genes (i.e., those assumed to play a role in the pharmacodynamics and pharmacokinetics of ADs). However, analysis of the polymorphisms of pharmacodynamic candidate genes involved in serotonin synaptic transmission (*SLC6A4*, *HTR2A*), neurotrophic activity (brain-derived neurotrophic factor [*BDNF*]), and catechol-O-methyltransferase (*COMT*) modulation revealed a small and poorly reproducible predictivity of AD response in patients with MDD (Fabbri *et al.* 2020). Recently, the rs1800532 polymorphism of the serotonin transporter gene (*SLC6A4*) was found to be correlated with both suicide vulnerability and poor response to lithium and clozapine, the only documented agents with antisuicidal properties (De Berardis *et al.* 2021).

Polymorphisms in pharmacokinetic genes responsible for antidepressant metabolism (*CYP2D6* and *CYP2C19*) have been found to affect the function of the corresponding enzymes, and a recent systematic review demonstrated that *CYP2D6* and *CYP2C19* pharmacogenetic testing may predict response to antidepressants in specific individuals; however, whether this will translate to improved or safer clinical outcomes remains unclear (Smith and Nemeroff 2020).

Furthermore, it is still debated whether genetic testing should be limited to patients exhibiting treatment unresponsiveness/sensitivity or whether the benefit

would be most marked if testing is conducted before the initiation of the first antidepressant (Zeier *et al.* 2018).

Genome-wide association studies (GWAS) compare the frequencies of SNPs between cases and controls to identify variants associated with the trait of interest. In general, GWAS have failed to identify polymorphisms associated with AD response in patients with MDD (Smith and Nemeroff 2020). (For a more detailed review, see Chapter 6, "Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics," in this textbook).

Because genetic studies thus far have returned results with limited clinical utility, it has been proposed that gene-by-environment interplay may be a factor influencing not only pathophysiology but also treatment response. *Epigenetics* refers to the molecular mechanisms that regulate gene expression in response to the environment without modification in the underlying DNA sequence. DNA methylation, the most stable type of epigenetic mechanism, consists in the addition of a methyl (CH_3) group to the carbon-5 of the cytosine moiety in the DNA sequence, generating the modified nucleotide 5-methylcytosine (5mC), which is involved in gene silencing. Two other major epigenetic mechanisms are posttranslational histone modification (which controls chromatin condensation and, by this mechanism, regulates gene expression) and regulation by noncoding RNA, particularly microRNAs.

Some studies suggest that antidepressants, at least partially, act by altering or even reversing epigenetic modifications and that the methylation status of some genes could predict the response to AD treatment in patients with MDD (Czarny *et al.* 2021). Specifically, *SLC6A4* (coding for the serotonin transporter) promoter hypomethylation has been linked with diminished response to escitalopram (Domschke *et al.* 2014) and with diminished dimensional and categorical response to SSRIs (Schiele *et al.* 2021). Of note, hypermethylation of the *SLC6A4* promoter has been associated with improved response to selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and fluvoxamine (Okada *et al.* 2014). However, because the data obtained in retrospective studies do not allow for differentiation between preexisting differences in DNA methylation (due to heredity and/or environmental factors) and those induced by the treatments, investigation with longitudinal designs is required.

Although it seems that the results of the remaining omics platforms (transcriptomics, proteomics, and metabolomics) indicate the possibility of developing actionable biomarkers for the selection of AD for MDD treatment, studies that support their application in clinical practice are lacking.

Brain Imaging

Structural and functional brain imaging has been explored as a putative index of treatment response in MDD. A recent systematic review (Enneking *et al.* 2020) demonstrated that larger pretreatment anterior cingulate cortex and hippocampal volumes are correlated with response to ADs and found that machine learning approaches based on pretreatment whole-brain patterns exhibited accuracies of 64%-90% in predicting AD response at the individual MDD patient level. Furthermore, altered connectivity of cingulum cingulate and stria terminalis tracts is predictive of remission after 8 weeks of treatment with escitalopram, sertraline, or venlafaxine (Porcu *et al.* 2018). However, despite the number of neuroimaging studies conducted on the AD response in MDD, the results are too inconsistent to produce predictors available in clinical practice.

Electroencephalographic Biomarkers

In comparison with brain imaging techniques, electroencephalography (EEG) is potentially more cost-effective and can be more feasibly and safely implemented in different clinical settings. Quantitative electroencephalography (QEEG) using standardized and reproducible mathematical algorithms enables the measurement of the alpha, theta, beta, and gamma patterns of rhythmic electrical activity and evoked potentials (i.e., the average brain response to a repeated stimulus). However, although a recent meta-analysis (Widge *et al.* 2019) concluded that QEEG was not clinically reliable for predicting depression treatment response owing to the methodological limitations of the then-existing studies, more recent publications are very promising indeed (Liu *et al.* 2020; Zhdanov *et al.* 2020).

Predicting Lithium Response in Bipolar Disorder

Bipolar disorder (BD) is a severe illness characterized by pathological mood swings, from depressive episodes to periods of elevated/irritable mood defining mania (BD type I) or hypomania (BD type II) episodes. Additionally, some patients with BD may experience mixed episodes in which various combinations of depressive and manic symptoms occur. BD treatment aims to stabilize mood and prevent future depressive and manic episodes. Lithium is the mainstay treatment for preventing mood relapses of any polarity and suicidal behaviors, and for treating acute manic episodes in patients with BD. However, among patients receiving lithium for at least 2 years, three subgroups have been consistently identified--complete responders, partial responders, and nonresponders--with about one-third of patients belonging to each group. For patients in the second and third subgroups, antipsychotics and antidepressants may be necessary as adjunctive therapy to attain euthymia (Vieta *et al.* 2011).

Sociodemographic and Clinical Predictors of Lithium Response

A recent systematic review and meta-analysis of 71 studies (Hui *et al.* 2019) identified six clinical predictors of good response to lithium therapy in BD: a mania-depression-interval course sequence, absence of rapid cycling and psychotic symptoms, family history of BD, shorter illness duration prior to lithium being prescribed, and later age at onset.

A further systematic review, including 34 studies (from 31 independent datasets) published between 1991 and 2018 (Grillault Laroche *et al.* 2020), reported sociodemographic and/or clinical variables associated with treatment response and/or with illness outcome during long-term lithium treatment ([?] 6 months). When the analysis of results was restricted to the 11 good-or borderline-good-quality studies, only the higher lifetime number of hospitalizations remained associated with a poor outcome for lithium prophylaxis, while no predictors of good outcome were identified.

The Pharmacogenomics of Bipolar Disorder (PGBD) study was a recent 11-site prospective trial designed to identify predictors of lithium response in patients with BD type I followed for up to 2 years (Lin *et al.* 2021). Significant clinical predictors of treatment failure included baseline anxiety symptoms, functional impairments, adverse life events, history of migraine, suicidal ideation/suicide attempts, and mixed episodes, as well as a chronic course of illness. Unlike the above-reported reviews, the

PGBD study found no evidence for an association of lithium treatment response with age at onset, number of hospitalizations, or rapid cycling (Lin *et al.* 2021).

Pharmacogenomics of Lithium Response in Bipolar Disorder

The candidate gene approach selects a putative gene based on its relevance in the postulated mechanism of the pathophysiology of the investigated disease and/or pharmacological response. None of the studies that explored a candidate genomic region evidenced a linkage between genetic markers at these loci and lithium response.

The lack of replicability of linkage studies that performed scans of the entire genome suggests that no major genes are involved in lithium response. Similarly, the candidate gene association studies on lithium response could not provide replicable associations between candidate genes or variants and lithium response (Senner *et al.* 2021).

Unlike candidate gene studies, GWAS are not based on a priori hypotheses. Some of the GWAS, which try to identify common genetic variants with small effect sizes throughout the genome in large populations that include cases and controls, have reported SNPs that showed significant associations with response to lithium. A recent study (Vecera *et al.* 2021) reviewed six GWAS on genetic variations related to lithium response and side effects in patients with BD. Variants associated with lithium response were found on genes *GADL1* and *GRIA2* regulating the glutamate system, which has been extensively implicated in mood disorder pathophysiology. In addition, SNPs on the spectrin domains 1 gene (*SESTD1*), which encodes a synaptic protein that directly binds to phospholipids, may account for lithium's ability to permeate cell membranes and mediate autoimmune and renal effects.

From a pharmaco-epigenetic point of view, increasing data have shown not only that antidepressants, mood stabilizers (anticonvulsants and lithium), and atypical antipsychotics modulate DNA methylation at promoters of genes involved in their targeted pathways but also that the observed effects can be associated with the pharmacological response. The first genome-wide association study of DNA methylation profiles in patients with BD, selected for their level of response to long-term treatment with lithium, identified seven differentially methylated regions with good discriminatory power between excellent response and nonresponse to lithium in patients with BD type I (Marie-Claire *et al.* 2020). However, it cannot be concluded that the epigenetic changes observed in the presence of a given drug are purely the effect of the drug and not the sum of this effect and other environmental factors that could modify DNA methylation. Further prospective studies that include environmental factors during the illness as well as treatment are needed to understand the potential use of DNA methylation as a predictive biomarker.

In conclusion, although GWAS have provided a powerful approach to addressing the main limitations of studies on candidate genes, replication of results in larger cohorts and different populations of patients with BD is needed.

Neuroimaging

A few longitudinal structural neuroimaging studies examined whether gray matter changes during lithium treatment correlate with lithium response. A positive clinical response in medication-naive patients with BD was associated with persistently increased cerebral gray matter volume throughout the 16-week lithium treatment (Lyoo *et al.* 2010). Similarly, a 4-week longitudinal study showed that BD patients

with a manic episode who responded to lithium had an increased prefrontal gray matter volume compared with those who did not respond (Moore *et al.* 2009). The relationship between response to lithium treatment in BD and task-based brain activation changes on functional MRI (fMRI) has been only sparsely investigated. A pilot study found greater activation to an emotional faces task in the prefrontal cortex and reduced activation in limbic regions in long-term lithium responders than in nonresponders (Rootes-Murdy *et al.* 2019).

Another fMRI measure, resting-state functional connectivity (RSFC), identifies functional connections between brain regions (not necessarily implying anatomical connectivity). Taylor *et al.* (2021) have reviewed studies on RSFC biomarkers of treatment response in mood disorders, including BD. Although cortico-limbic connectivity is implicated across studies, no single biomarker replicated in multiple independent datasets has been found.

Electroencephalographic Biomarkers

Some studies analyzing the relationship between EEG and lithium response suggested that patients with electroencephalographic abnormalities were more likely to respond to valproate than lithium (Ikeda *et al.* 2002). Other studies investigated the event-related potentials as possible predictors of lithium response. In both cases, the few studies and the small patient populations investigated prevented the possibility of drawing any firm conclusions (Tighe *et al.* 2011).

Predicting Antipsychotic Drug Response in First Episode of Psychosis

Schizophrenia is a severe disorder presenting psychotic symptoms, such as hallucinations and delusions, and cognitive deficits. Because attaining a clinical and functional improvement in patients in their first episode of psychosis (FEP) is critical to producing a positive long-term illness outcome, identifying factors predicting treatment response in the early phase of the disease is the focus of much research.

Long-term use of atypical antipsychotics is the first-line treatment in schizophrenia. However, even during the FEP, when the response to antipsychotics tends to be greater, up to one-quarter of patients show persisting symptoms of schizophrenia (Schennach *et al.* 2012). Clozapine is effective in patients who have not responded to other antipsychotics but carries the risk of serious side effects and requires regular blood monitoring; thus, identifying predictive biomarkers of clozapine response may aid in the early initiation of clozapine treatment.

Sociodemographic and Clinical Predictors of Antipsychotic Response in FEP

In patients experiencing their FEP, gender and marital status are controversial predictors of antipsychotic response (Bozzatello *et al.* 2019), while poor premorbid adjustment and lower educational level predict a worse drug treatment response. Clinical predictors of treatment resistance and poor outcome in adults and children with FEP include higher severity of negative symptoms at baseline (Demjaha *et al.* 2017; Downs *et al.* 2019) and comorbidity with substance use disorders--in particular, cannabis (Pelayo-Teran *et al.* 2014).

A 10-year longitudinal study (Demjaha *et al.* 2017) revealed that in the great majority of patients with treatment-resistant schizophrenia, the resistance is present from the illness onset. Negative symptoms, younger age at onset, and longer duration of untreated psychosis predicted treatment resistance.

In a recent review of prospective longitudinal studies (Smart *et al.* 2021), out of the seven studies that tested the age at onset as a response predictor, six reported that younger age at onset predicted treatment-resistant FEP.

Pharmacogenetics

Antipsychotics mainly bind to dopamine D$_2$ and serotonin 5-HT$_{2A}$ receptors. However, studies linking genetic variation in *DRD2* to antipsychotic efficacy or adverse reactions have been inconsistent (Yoshida and Muller 2020). Several studies reported that the serotonin 5-HT$_{1A}$ receptor gene (*HTR1A*) polymorphism rs6295 was significantly associated with a clinical improvement with second-generation antipsychotics, but further studies using larger sample populations are required to confirm this effect (Takekita *et al.* 2016). Some studies support the involvement of glutamate gene polymorphisms in response to risperidone in FEP patients (Stevenson *et al.* 2016) as well as in an early (2-week) response to risperidone, which is a good indicator of subsequent pharmacological outcome (Sacchetti *et al.* 2017). Overall, evidence pointed to a role for the serotonin (5-HT_{2A} and 5-HT_{3A}; *HTR2A* and *HTR3A*), dopamine (D_2; *DRD2*), and glutamate system (glycine transporter 1; *SLC6A9*) genetic variants in clozapine response (Taylor *et al.* 2017; Zai *et al.* 2018).

Although some genetic tests (e.g., response to clozapine and risperidone) are commercially available, their clinical validity and utility have not been systematically evaluated or reported in published randomized clinical trials.

It is known that antipsychotics can induce the alteration of the methylation status of genes coding for their targeted pathways. Some methylation patterns existing before the use of antipsychotics can affect the efficacy of these medications (Tang *et al.* 2014; Zai *et al.* 2018), but our understanding of their contributions in schizophrenia is still in its infancy.

Neuroimaging

Structural neuroimaging studies have indicated that a reduced gyrification (a marker of normal cortical development) across multiple brain regions (Palaniyappan *et al.* 2013) is associated with poor response to antipsychotic treatment in patients with FEP. In contrast, a thinner cortex at baseline in antipsychotic-naive FEP patients predicted more robust clinical and cognitive improvement with clozapine and risperidone (Molina *et al.* 2014). In addition, drug-naive or minimally treated FEP patients with a larger pituitary volume at baseline showed less improvement in positive and overall psychotic symptoms during the initial 12 weeks of treatment with quetiapine (Garner *et al.* 2009).

Prospective studies have found that greater prefrontal cortical volumes prior to antipsychotic treatment are associated with a better response to clozapine. Accordingly, responders to clozapine had higher baseline perfusion and metabolic rate in the dorsolateral prefrontal cortex compared with the nonresponder group (Rodriguez *et al.* 1997; reported in Samanaite *et al.* 2018). However, it is unclear whether prefrontal structural integrity/activity may be specifically predictive of clozapine response or is a nonspecific prognostic factor.

RSFC showed that in medication-naive patients with FEP, greater default mode network (DMN) connectivity indices were associated with a more favorable subsequent response to antipsychotic treatment (Maximo *et al.* 2021). The DMN, which includes brain areas that are functionally and structurally connected (portions of frontal and posterior midline regions and the inferior parietal lobe), is a brain network suppressed during goal-directed activity and active during rest. Because the strength of connectivity within the DMN is thought to reflect the integrity of white matter tracts that connect these regions, this finding adds to the previous literature supporting the concept that white matter integrity has potential utility in predicting antipsychotic treatment response (Crossley *et al.* 2017)

Unfortunately, the paucity of longitudinal neuroimaging studies in this area makes it impossible to draw conclusions about their predictive value in clinical practice.

Electroencephalographic Biomarkers

A few studies have investigated electrographic baseline indices as possible predictors of response to antipsychotic drugs. A greater amount of fast activity has been described in patients who were responsive to antipsychotics compared with those who were resistant, while a predominance of alpha activity has been found in patients with a poor response to antipsychotic drugs. However, the ability of these indices to predict clinical response in individual subjects was not demonstrated (Mucci *et al.* 2006).

Application of PMIP in Other Disorders

Posttraumatic Stress Disorder

PTSD develops in some individuals after exposure to a traumatic event. The main clinical features of PTSD are the reexperiencing of the event, avoidance of trauma-related triggers, hyperarousal, and negative mood/cognitions. Currently, studies of personalized approaches to the treatment of PTSD are limited to psychotherapeutic interventions (Szeszko and Yehuda 2019), and no investigations on prediction of response to pharmacological treatments are available.

Anxiety Disorders

In the last two decades, several studies have investigated the response prediction to current pharmacological treatments in the three most common and debilitating anxiety disorders, namely, panic disorder, generalized anxiety disorder, and social anxiety disorder.

Unfortunately, investigation of clinical characteristics and neurobiological, genetic, and epigenetic markers in these disorders has thus far demonstrated only a marginal role in predicting treatment response and does not appear to be translatable to clinical practice (Perna *et al.* 2020b).

Recently, a first step toward personalized therapy for panic disorder, based on some phenomenological profiles (i.e., respiratory, cardiac, vestibular, and derealization/depersonalization), has been proposed (Caldirola and Perna 2019).

Conclusion and Future Directions

The aims of the personalized medicine approach are to achieve an accurate diagnosis and select the best therapeutic option for each person by integrating clinical, biological, and environmental factors. The development of personalized medicine in psychiatry is difficult because of the intrinsic complexity of psychiatric diseases. PMIP is based on the collection of very-large-scale data (big data) that are analyzed using advanced computational tool kits capable of making a prediction from such information. Information and communications technologies, such as mobile phones and wearable devices, allow for discreet monitoring of behavioral, physiological, and cognitive/emotional factors in ecological settings. Thus far, data obtained from clinical assessment, omics platforms, pharmacogenomics, neuroimaging, and EEG do not support the application of the PMIP approach in clinical practice.

Since the completion of the Human Genome Project in 2003, progress on the predictability of pharmacological treatment response and side effects based on patients' genetic signatures has been much slower than initially expected. Such a delay is partially due to the involvement of multiple genes in a patient's response to drugs, making it unlikely that a simple pathway from the gene to the pharmacological response will be found. This drawback prompted the development of new methodological approaches that take into account the complex polygenic architecture of antidepressant efficacy. For example, polygenic risk may be well utilized to estimate the multi-allelic contribution to antidepressant efficacy, providing an estimation of the individual genetic risk of developing a specific trait (e.g., antidepressant response).

International collaborations to increase sample size and the high-throughput nature of omics technologies, as well as recent developments in machine learning (time-series techniques, methods based on Bayesian hierarchical models, and matrix factorization techniques), promise to achieve the final goal of developing an individual-level personalized psychiatry. The ultimate frontier of PMIP could be cell culture models, in which psychiatric disorders are manifestations of the donor's individual genetics and environmental interaction.

The generation of induced pluripotent stem cells (iPSC) from patients with a variety of single-gene or complex-inheritance diseases provides an unprecedented opportunity to recapitulate the pathological human tissue formation in vitro, thereby enabling disease investigation and drug development.

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CHAPTER 9

Machine Learning in Psychopharmacology

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Psychopharmacology focuses on mechanistic explanations and subsequent interventional approaches to psychiatric illness (Wang and Krystal 2014). Consistent with pharmacology more broadly, modern psychopharmacology is increasingly focused on targeted and personalized treatment options (Chekroud *et al.* 2017; Stahl 2008). With mechanistic explanations of psychiatric illness evolving to take into account expanding layers of research (i.e., genomics, epigenomics, proteomics, neuroimaging, electrophysiology), the subsequent interventional approaches are subject to further personalization through development of more sensitive, objective, and patient-specific measurements of mental health and illness (Galatzer-Levy and Galatzer-Levy 2007; Insel *et al.* 2010; Wang and Krystal 2014). To achieve this, there is an emerging reliance on advanced computational methods grounded in machine learning. In this chapter, we provide a brief summary of statistical approaches in psychopharmacology, summarize general machine learning approaches and the problems in psychopharmacology they are well suited to address, and provide examples of where such approaches have been useful in clinical research and patient care.

History of Statistical Approaches in Psychopharmacology

Classical Statistical Approaches in Psychopharmacology

The 1970s and 1980s saw a movement in psychiatric diagnosis away from theoretical study of mental illness and toward an increasingly scientific approach grounded in

observable phenomena. This shift to the use of scientific methods eventually led to a major revision of DSM, in which diagnosis became grounded in observable symptomatology (Galatzer-Levy and Galatzer-Levy 2007), as research on psychiatric illness sought to develop a methodology that would allow scientists to carefully separate relevant symptoms and direct effects of treatment from the noise of patients' interpersonal and environmental surroundings.

In the context of development of novel treatments, the focus shifted to outcome measures that would facilitate statistical hypothesis testing as a methodology to determine treatment efficacy. Such testing allowed researchers to arrive at, for the first time, a common understanding of psychiatric treatment effects through "standardized" research methodologies, measures, and mathematical language. This shared understanding laid the groundwork for the modern clinical trial in psychiatry.

Clinical trials largely follow the methodology proposed by Ronald Fisher (Stigler 1986), in which the impact of an intervention is assessed as the covariance between the independent and dependent variables (Fisher 1921). Analysis of variance (ANOVA), also introduced by Fisher, allows researchers to formally compare the average effects of an independent variable on a dependent variable and provide a probabilistic estimate that the observed difference in conditions is statistically meaningful. With the emergence of standardized outcome measures in psychiatry, the classical clinical trial design could now be applied to evaluate novel interventional compounds in a manner that had not been possible before.

Limitations of Classical Statistical Approaches in Psychopharmacology

Fisher's approach, which also introduced common statistical concepts such as a *P* values, came with two caveats, with both having considerable effects on the utility of this approach in psychopharmacology. First, for Fisher's statistical approach to work, all variables other than the independent and dependent variables must be held constant. Focusing on a single main effect is particularly challenging in psychopharmacology, which aims to demonstrate *effectiveness* of treatment in messy real-world contexts over efficacy in tightly controlled scenarios (Goldberg and Stahl 2021). Second, Fisher's approach only aimed to test (i.e., confirm or reject) a *null hypothesis* that the different experimental conditions are the same. This approach, while valuable for testing a scientific hypothesis for the first time, does not allow one to make a prediction about future events. Put another way, this means that traditional statistical approaches are well suited to rigorous testing of whether a compound had an effect on a population *over chance*, but they are not designed to make predictions on correct dose or course of treatment, which are necessary for development of personalized treatments.

Limitations of Psychiatric Nosology for Application of Statistical Approaches

Another major barrier in the development of personalized treatments in psychopharmacology is the existing psychiatric nosology, which is neither personal nor specific. The measurement scheme underlying DSM diagnoses has limitations that preclude it from being a viable tool to assess sensitive and specific effects of treatment (Galatzer-Levy and Bryant 2013). First, the summation of individual symptom measurements to determine whether a patient's presentation meets criteria for a particular disorder assumes that individual symptoms are equally weighted, but there is strong evidence against this being the case. Second, DSM intentionally avoids mechanistic explanations of psychiatric illness. The fact that there is no evidence that symptoms are causally related to one another places any method that combines them on shaky logical ground. Third, given that some but not all symptom criteria are required to be met, a pool of individuals who share a diagnosis may be shockingly heterogeneous in their symptom presentation. Simultaneously, many diagnoses are often comorbid and responsive to similar treatments, casting doubt on the discrete nature of psychiatric illness classifications. The lack of specificity in outcome definitions has consequences for psychopharmacology. Targeted treatments are more likely to succeed when they are focused on individual symptoms (e.g., motor functioning, circadian rhythm, cognition) rather than on disease classifications (e.g., major depressive disorder, PTSD, autism spectrum disorder).

In short, modern psychopharmacology is presented with two fundamental problems. First, the mathematical approach to making decisions about cause and effect does not allow for the diversity of inputs necessary for prediction that enables personalization. Second, outcome measures in psychiatry are not sensitive enough to measure the current class of treatment compounds, which are targeted toward neurological pathways with broad downstream effects. Machine learning introduces potential solutions to both of these fundamental problems.

Machine Learning and Its Applications in Personalized Psychopharmacology

Machine learning broadly refers to the practice of learning patterns from data to improve performance and make predictions (Galatzer-Levy 2014). Machine learning algorithms attempt to identify complex relationships between variables. Personalized medicine has three primary classes of problems (Statnikov *et al.* 2011):

1. Given a patient, can we predict disease type or subtype?

2. Given a patient, can we predict the correct treatment?
3. Given a patient, can we predict the correct dosage of treatment?

Rather than exhaustively summarizing machine learning methods, we summarize approaches to address each of the questions above as they relate to psychopharmacological drug development and utilization.

Can We Predict Disease Type or Subtype?

DSM provides a framework in which symptoms cluster into disorders or subtypes of disorders based on a set of decision rules and cutoff points. The DSM approach can be considered an algorithmic approach to classification. In this subsection, we discuss empirical approaches to defining clinical populations/subpopulations.

Unsupervised Learning

Unsupervised machine learning refers to a class of algorithms that draw inferences about the relationship between variables in the absence of a label (Galatzer-Levy and Galatzer-Levy 2007; Bernardo and Smith 2001). As a general example, unsupervised machine learning could be used to group individuals according to their level of severity on one or more clinical indicators. Similarly, researchers can cluster patients on the basis of behavioral characteristics and presentation of symptoms (Scholz 2014). Importantly, they can do this without needing an a priori definition of a diagnostic status. Unsupervised machine learning models allow for dimensionality reduction (Barlow 1989), which is useful in psychiatry, where high-dimensional data from behavioral quantifications and symptom measurements must be evaluated simultaneously. Ultimately, unsupervised machine learning allows for the clustering of populations into subgroups without the need for arbitrary decision rules and cutoff points.

One commonly used approach is *mixture modeling*, which relies on identifying *latent* (or not directly observable) populations by identifying underlying mixture distributions (Mori *et al.* 2020). The mathematical approach to clustering in this way does not differ significantly from feature reduction approaches. However, instead of asking how variables cluster together within people, one seeks to identify how people cluster together on variables (Muthen and Muthen 2000). Examples of this include empirical identification of disease subgroups in major depressive disorder (Ulbricht *et al.* 2018), PTSD (Campbell *et al.* 2020), and autism spectrum disorder (Dekker *et al.* 2021). This technique is not limited to the clustering of symptom profiles alone. Researchers can identify symptom profiles that cluster with comorbidities, functional impairment, and population-level characteristics. Empirical identification of these subtypes allows for development and facilitation of personalized treatment (Grant *et al.* 2020).

Graphical/Network Models

A limitation of models that include complex dependencies across a large number of variables is that they are difficult to interpret. Graphical models provide a framework for representing multidimensional relationships in two-dimensional space to aid in interpretation and, in some instances, hypothesis testing (Muthen 2004). Although the mathematical basis of such models may vary (most commonly between Bayesian networks and Markov random fields), the underlying concepts are similar (Galatzer-Levy *et al.* 2017a). Researchers can derive the structure of multiple related variables by algorithmically testing conditional dependencies between all variables of the model. Graph models are increasingly utilized in stress pathology research to better understand how multiple relevant dimensions relate to one another. A number of recent publications have examined how certain symptoms such as complicated grief (Malgaroli *et al.* 2022), comorbid depression and obsessive-compulsive behavior (McNally *et al.* 2017), and PTSD (Galatzer-Levy *et al.* 2017b) relate causally.

Supervised Learning

Supervised machine learning is a class of data modeling that is concerned with the development of algorithms that can learn a function applied to the data that optimally predicts an outcome (Singh *et al.* 2016). These models fall into two classes: *classification models*, which attempt to predict a categorical outcome (e.g., healthy vs. ill based on behavioral and symptom features), and *regression models*, which attempt to predict a continuous outcome (e.g., symptom severity reduction in response to treatment). Classification models have particular relevance to predicting disease type or subtype. Their benefit is similar to that of unsupervised machine learning models in that they

do not require arbitrary cutoff points or thresholds to predict--using a set of features (i.e., symptoms, observed behavior)--a diagnosis. They are distinct from unsupervised models in that the relationship between the features and the ultimate classification (i.e., the diagnosis) is *learned* from existing data.

Can We Predict the Correct Treatment?

As previously discussed, traditional null hypothesis testing is not designed to make predictions. Rather, the goal of those statistical methods is to establish association to confirm or disconfirm a scientific hypothesis. While this is of great value, the next logical question is how to apply the field's accumulated knowledge to make an accurate clinical decision about a specific patient (Bzdok *et al.* 2021).

Unsupervised Learning

Often, the most relevant patient characteristic is their pattern of response to treatment. Traditional approaches to defining meaningful change over time (e.g., 30% reduction in symptoms, change in diagnostic status) lack a clear empirical basis. The use of latent variable approaches to characterize individuals within a population that are similar to one another in their level of symptom severity (intercept) and change over time (slope) is commonly known as *latent growth mixture modeling* (Jung and Wickrama 2008). Latent growth mixture modeling has relevant applications to treatment personalization in psychopharmacology. By identifying individuals' predictive profile in response to varied treatments, clinicians can identify individuals more likely to respond to specific treatments, such as different classes or combinations of antidepressants (Stulz *et al.* 2010).

Graphical/Network Models

After graphical models are identified, they can be used for purposes beyond description of observed patient characteristics, such as to better understand treatments that can be utilized. After determining the relationships between variables in a graph, researchers can conduct experiments to set the value of a particular variable to determine its downstream effects on other variables of interest (Statnikov *et al.* 2011). For example, a researcher who has derived a graphical model of a gene expression network may want to know how downstream expression patterns are affected, if at all, when they alter the value of a particular target with a drug. Such an experiment allows the researcher to develop hypotheses on drug effects before collecting experimental data.

Supervised Learning

Classification machine learning models also have particular relevance to prediction of correct treatment. Various approaches are used to identify and validate complex dependencies between variables using Boolean logic (AND, OR, NOT), as well as absolute conditionality (IF, THEN, ELSE) and conditional probabilities (probability of x given y). Because the relationships between variables may be nonlinear, these methods utilize computational optimization methods to identify models that are dependent on more variables than traditional statistics would allow (Kotsiantis *et al.* 2007). Once a model has been identified that combines variables to predict, for example, a treatment expected to be effective, that model can be applied to new data to make a prediction about a new case. Such a model could be embedded in software, and clinicians could enter those variables and receive a prediction of the kind of treatment most likely to be successful.

Can We Predict the Correct Dosage of Treatment?

Supervised Learning

Thus far, we have discussed the use of classification models in identifying patient subtypes and predicting effective treatment regimens. Regression models, which are another form of supervised models, have particular relevance in the prediction of dosage given their ability to make a prediction based on continuous variables rather than discrete or binary variables.

In theory, all patients in a population should demonstrate uniform treatment effects given random variability around the average response. However, multiple known and hidden variables impact the relationship between outcomes and the influencing variables. To effectively dose treatment, researchers must be capable of accurately predicting response to treatment, because these influencing variables (and likely several more) vary across the population. In psychiatry, this is often a trial-and-error approach involving one or more medications to optimize for therapeutic effect while minimizing side-effect profiles. The goal of a regression model is the same as the goal of the treating clinician: to make an accurate prediction of the degree of response based on a set of variables, both therapeutic and nontherapeutic. The challenge is the complexity of the relationships between the input variables.

Regression models can vary in complexity from linear models with simpler relationships between a few input variables to nonlinear models with complex relationships between several variables. For the latter, regularized regression techniques such as LASSO (Least Absolute Shrinkage and Selection Operator), ridge, and elastic net regression are useful because they allow the data analyst to select the preferred level of model complexity, from linear to highly nonlinear (Hans 2009). Increased complexity of a model can easily lead to overfitting. Regularized regression models include a *regularization term*, which imposes a penalty as models increase in complexity, making model fit harder to achieve as the complexity of the model increases (Xu *et al.* 2009). The coefficients of variables not relevant to the model are shrunk to minimize their impact on the model. Algorithmic identification of features that have little or no effect allows analysts to use these models for feature selection, as the most relevant variables will be selected into the model. One of the key benefits of regularized regression models is that they are highly interpretable because they provide evidence for which variables are predictive as well as the degree to which they contribute to overall predictive accuracy.

Regression-based machine learning techniques may become more relevant as the field moves toward targeting specific phenotypes or side effects typically measured using continuous indicators of functioning, such as cognitive ability, functional impairment, biological activity, or digital measurements (Abbas *et al.* 2021; Insel 2014). Such techniques have particular application in the early phases of research, including in nonclinical populations, where researchers may be interested in determining a dose-response relationship. Similarly, regression-based machine learning may become increasingly relevant as treatments aim to target specific phenotypes such as cognitive impairment, negative symptoms in schizophrenia, mood and anhedonic behavior in depression, or states of hyperarousal in anxiety disorders or PTSD (Galatzer-Levy *et al.* 2018). The use of regression models opens the door to solving multiple precision medicine problems, including individual titration of medication, prediction of high-level drug interactions, and prediction of nonclinical endpoints, all of which are relevant to psychiatry.

Limitations of Machine Learning and Its Application in Psychopharmacology

Machine learning models are powerful tools that can be used to make decisions about patient diagnosis and course of treatment. However, as with all tools available to researchers and clinicians, misapplication of those tools can lead to erroneous conclusions and dangerous consequences.

Overfitting Models

Unlike traditional statistical approaches that are meant to test specific hypotheses about the linear relationship between inputs and outcome, machine learning aims to *learn* the relationship between inputs and outcome, including the dimensional nature of the underlying relationship. As machine learning algorithms search for such relationships, they are prone to *overfit* the models, so that the solution does not generalize beyond the data that they are being trained on. There are two main solutions to this. The first is to use an additional parameter in the machine learning model we touched on earlier (i.e., the loss function). A loss function is akin to calculation of error in the model: well-fit models will demonstrate both strong model fit and low loss estimates. The second solution is to use cross-validation to determine whether the model is overfitted. Cross-validation consists of randomly splitting the training data into multiple training/testing parts. The machine learning researcher will train a model on a subset of the data they have access to (training data) and then test the model's ability to make predictions on a holdout dataset (testing data). Cross-validation involves repeating this process on multiple random splits of testing and training data so as to not overfit the model to any one iteration of the training data. This approach allows the researcher to determine whether the model was simply fit to the pool of data it was trained on or whether it generalizes across the dataset.

Bias in Machine Learning

Although randomly splitting training and testing data guards against mathematical overfitting that results in poor generalization of the model beyond the data it was trained on, this approach does not establish the generalizability and robustness of the machine learning algorithm in the real world. For example, if characteristics such as gender, race, and other key variables are not part of a dataset, any algorithm trained on that dataset will not be accurate when making predictions for a population that it was not trained on. Issues of bias are an important reason that machine learning algorithm development--within medicine and beyond--must be conducted with expertise in human subject research, because such issues cannot simply be addressed algorithmically; rather, they reflect biases inherent in the data used. It is equally important for the scientific and medical communities to understand that complex predictive models are only as relevant as the underlying data they were trained and tested on and that a concerted effort needs to be made to avoid reinforcing existing societal biases.

"Black-Box" Models and Model Updates

The term *black box* is often used to refer to the inability of a researcher or clinician to observe *how* the algorithm made a decision. It is a misnomer that the information is not available; rather, it may simply be beyond human comprehension given the dimensionality in which the relationship may have been observed by the algorithm. Increasingly, there have been attempts to add visualization layers that aid humans in interpreting complex relationships, known as *explainable artificial intelligence* (Samek *et al.* 2019). Explainable artificial intelligence is of particular importance in medicine, where both researchers' and clinicians' goals are not just to address the problem at hand but also to better understand the disease pathogenesis and to learn and expand the knowledge base in the medical community.

In certain scenarios, models are truly opaque to the researcher or clinician. With the rapid growth of interest in the use of remote monitoring in patient care and clinical research, the use of commercial devices has greatly increased. It is often assumed that all heart rate monitors embedded in wrist wearables, for example, are equivalent or that, at a minimum, the same device is consistent over time. However, sensor-based health measures, which often rely on machine learning models, are only providing estimates. Changes to the manner in which the device is used or updates to the algorithms can alter those estimates. The lack of transparency in the configuration of hardware and signal processing methods represents a significant challenge, especially in clinical research, because regulatory organizations such as the FDA have traditionally only leaned on clinical scales that are transparent, are rarely updated, and require new validation when they are updated (Benjamens *et al.* 2020).

Conclusion

The role of machine learning in psychopharmacology, psychiatry, and mental health care more broadly remains in its infancy when one considers the impact that it can have on clinical research and patient care. New approaches open up new opportunities but also introduce new risks. For psychiatry to improve patient outcomes by providing the right treatment at the right time to the right patient, it requires not only research to determine this level of personalized need but also approaches to decision making that are capable of such sophisticated calculations. Treatment development in psychopharmacology and psychiatry has relied on methods that identify average effects across heuristically defined clinical phenotypes. As the field moves toward narrow and specific phenotypes along with treatments that are matched to, and target these phenotypes, there is equally a need for data-analytic approaches to achieve these new goals. Development of such approaches represents the unrealized promise of machine learning in psychopharmacology.

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PART II

Classes of Psychiatric Treatments

Antidepressants and Anxiolytics

CHAPTER 10

Monoamine Oxidase Inhibitors

K. Ranga Rama Krishnan, M.D.

History and Discovery

Monoamine oxidase inhibitors (MAOIs) were first identified as effective antidepressants in the late 1950s. An early report suggested that iproniazid, an antitubercular agent, had mood-elevating properties in patients who had been treated for tuberculosis (Bloch *et al.* 1954). Following these observations, two studies confirmed that iproniazid did indeed have antidepressant properties (Crane 1957; Kline 1958). Zeller (1963) showed that iproniazid caused potent inhibition of monoamine oxidase (MAO) enzymes both in vivo and in vitro in the brain. He also reported that the medication reversed some of the actions of reserpine. Because reserpine produced significant depression as a side effect, it was suggested that iproniazid might have mood-elevating properties.

The use of iproniazid soon fell into disfavor because of its significant hepatotoxicity. Other MAOIs, both hydrazine derivatives (e.g., isocarboxazid, phenylhydrazine) and nonhydrazine derivatives (e.g., tranylcypromine), were introduced. These MAOIs were not specific for any subtype of MAO enzyme, and they were irreversible inhibitors of MAO (see next section, "Monoamine Oxidase"). Their use has been somewhat limited because hypertensive crisis by the MAOIs may occur in some patients from potentiation of the pressor effects of amines (such as tyramine) in food (Blackwell *et al.* 1967).

In more recent years, there has been a resurgence of interest in the development of new MAOIs--that is, in development of MAOIs that are more selective for specific subtypes of MAO enzyme and that are reversible in nature. Reversible monoamine oxidase A (MAO-A) inhibitors, such as moclobemide, have been introduced in Europe but are not available in the United States. Newer MAOIs, such as selegiline, a monoamine oxidase B (MAO-B) inhibitor, have been introduced. Table 10-1 classifies the MAOIs by structure, selectivity, and reversibility.

TABLE 10-1. Classification of monoamine oxidase inhibitor drugs by structure, selectivity, and reversibility

Drug	Hydrazine	Selective	Reversible
Phenelzine	Yes	No	No
Isocarboxazid	Yes	No	No
Tranylcypromine	No	No	No
Selegiline	No	Yes[a,b]	No
Rasagiline	No	Yes[a,b]	No
Safinamide	No	Yes[a,b]	Yes
Clorgyline[c]	No	Yes[d]	No
Moclobemide[e]	No	Yes[d]	Yes
Brofaromine[c]	No	Yes[d]	Yes

[a] Selective for monoamine oxidase B (MAO-B) at lower dosages.

[b] Becomes nonselective at higher dosages.

[c] Never marketed in the United States.

[d] Selective for monoamine oxidase A (MAO-A).

[e] Not commercially available in the United States.

Monoamine Oxidase

A and B Isoenzymes

MAO is widely distributed in mammals. Two isoenzymes, MAO-A and MAO-B, are of special interest (Cesura and Pletscher 1992). Both are present in the CNS and in some peripheral organs. For example, MAO-A is present in the liver, heart, and pancreas, and MAO-B is present in the liver, posterior pituitary, renal tubules, and endocrine pancreas (Saura *et al.* 1992). Both MAO-A and MAO-B are present in discrete cell populations within the CNS. MAO-A is present in both dopamine and norepinephrine neurons, whereas MAO-B is present to a greater extent in serotonin (5-HT)-containing neurons. Both are also present in monoaminergic neurons in various subcortical regions of the brain. Glial cells also express MAO-A and MAO-B (Cesura and Pletscher 1992).

The physiological functions of these two isoenzymes have not been fully elucidated. The main substrates for MAO-A are epinephrine, norepinephrine, and 5-HT. The main substrates for MAO-B are phenylethylamine, phenylethanolamine, tyramine, and benzylamine. dopamine and tryptamine are metabolized by both isoenzymes. The localization of the MAO subtypes does not fully correspond to the neurons containing the substrates. The reason for this discrepancy is unknown. The occurrence of the MAO-B form in 5-HT neurons may actually protect those neurons from amines (other than 5-HT) that could be toxic to them (Cesura and Pletscher 1992).

The primary structures of MAO-A and MAO-B have been fully described. MAO-A has 527 amino acids, and MAO-B has 520 amino acids. About 70% of the amino acid sequence of the two forms is homologous. The genes for both isoenzymes are located on the short arm of the human X chromosome. *MAO-A* and *MAO-B* are linked and have been located in the XP11.23-P11 and XP22.1 regions, respectively. The genes span about 70 kilobases (kb) and consist of about 15 exons and 14 introns. *MAO-A* has two messenger RNA (mRNA) transcripts of 2.1 and 5.0 kb in length. *MAO-B* has a 3-kb mRNA single transcript (Cesura and Pletscher 1992). A rare inherited disorder, Norrie's disease, is characterized by deletion of both genes; patients with this disorder have very severe mental retardation and blindness. Another rare inherited disorder is Brunner syndrome, caused by a mutation in *MAO-A*. It is characterized by impulsive aggressiveness and mild mental retardation (Brunner *et al.* 1993).

The subunit composition of MAO is unknown. The enzyme is primarily found in the outer mitochondrial membrane; flavin adenine dinucleotide is a cofactor for both MAO-A and MAO-B.

Because the cofactor domain is the same for both of the MAO isoenzymes, the structural differences responsible for substrate specificity are believed to lie in regions of the protein that bind to the hydrophobic moiety of the substrate. Although dopamine is considered to be a mixed substrate for both MAO-A and MAO-B, the breakdown of dopamine in the striatal regions of the brain is preferentially by MAO-B. In other regions, MAO-A may be more important. There may be regional differences as to which isoenzyme is responsible for the metabolism of other biogenic amines that are substrates for both forms of MAO (Cesura and Pletscher 1992). MAO-A levels are higher than MAO-B in infants, but this reverses with aging (Tong *et al.* 2013).

Enzyme Kinetics

The enzyme kinetics of MAO enzymes are complex and depend on the nature of the substrate. MAO-A and MAO-B have different intrinsic catalytic rates (Ramsay and Albreht 2018). Some substrates (e.g., tyramine) go through ping-pong mechanisms characterized by oxidation of the amine to the imine form, which is subsequently released from the reduced enzyme before reoxidation occurs. Other substrates (e.g., benzylamine) involve formation of a tertiary complex with the enzyme and oxygen (Husain *et al.* 1982; Pearce and Roth 1985; Ramsay and Singer 1991). The complex kinetics are influenced by oxygen levels and depend on the amine substrate (Ramsay and Albreht 2018).

Positron Emission Tomographic Studies of MAO-A in Psychiatric Disorders

[^{11}C]Harmine is a selective reversible PET radiotracer with high brain uptake that binds with high affinity to MAO-A. A study using this tracer reported highly significant elevations in brain MAO-A binding during episodes of major depressive disorder that persisted even after selective serotonin reuptake inhibitor (SSRI) treatment (Meyer *et al.* 2009). Interestingly, subjects with higher MAO-A levels had a higher rate of major depressive episode recurrence (Meyer *et al.* 2009).

Mechanism of Action

The target function of MAOIs is regulation of the monoamine content within the nervous system. Because MAO is bound to the outer surface of the plasma membrane of the mitochondria, in neurons MAO is unable to deaminate amines that are present inside stored vesicles and can metabolize only amines that are present in the cytoplasm. As a result, MAO maintains a low cytoplasmic concentration of amines within the cells. Inhibition of neuronal MAO produces an increase in the amine content in the cytoplasm.

Initially, it was believed that the therapeutic action of MAOIs was a result of this amine accumulation (Finberg and Youdim 1984; Murphy *et al.* 1984, 1987). More recently, it has been suggested that secondary adaptive mechanisms may be important for the antidepressant action of these agents.

After several weeks of treatment, MAOIs produce effects such as reductions in the numbers of b-adrenoreceptors, a_1- and a_2-adrenoreceptors, and serotonin type 1 (5-HT_1) and serotonin type 2 (5-HT_2) receptors. These changes are similar to those produced by long-term use of tricyclic antidepressants (TCAs) and other antidepressant treatments (Da Prada *et al.* 1984, 1989).

MAOIs can be subdivided on the basis of not only the particular type of enzyme they inhibit but also the type of inhibition they produce (reversible or irreversible). The reversible MAOIs are basically chemically inert substrate analogs. MAOIs are recognized as substrates by the enzyme and are converted into intermediates by the normal mechanism. These converted compounds react to the inactive site of the enzyme and form a stable bound enzyme. This effect occurs gradually, and there is usually a correlation between the plasma concentration of the reversible inhibitors and pharmacological action.

Pharmacological Profile

The classic MAOIs inhibit both forms of the enzyme and are divided into two main subtypes: hydrazine and nonhydrazine derivatives (Figure 10-1). The hydrazine derivatives, two of which are currently available (phenelzine and isocarboxazid), are related to iproniazid. One nonhydrazine derivative, tranylcypromine, is commercially available.

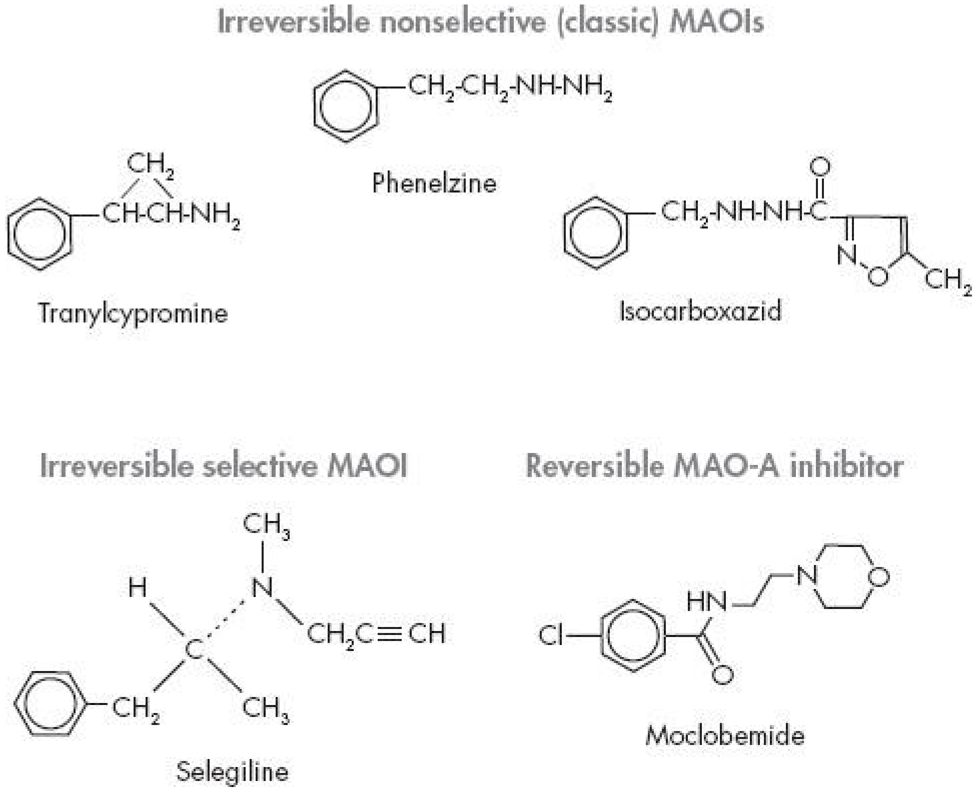
Irreversible nonselective (classic) MAOIs
CH2-CH2-NH-NH2
Phenelzine
CH2
CH-CH-NH2
Tranylcypromine
CH2-NH-NH-C
O
N
O
CH3
Isocarboxazid
Irreversible selective MAOI
CH3
N
H
C
CH2C≡CH
CH2
CH3
Selegiline
Reversible MAO-A inhibitor
HN
N
O
Cl
O
Moclobemide

FIGURE 10-1. Chemical structures of monoamine oxidase inhibitors (MAOIs).

Among the selective MAOIs, clorgyline (which was never marketed in the United States) is an example of an irreversible inhibitor of MAO-A, whereas selegiline is an irreversible inhibitor of MAO-B. Moclobemide is the only reversible inhibitor of MAO-A on the market (available in the United Kingdom and Australia, but not in the United States).

Three classic MAOIs (i.e., phenelzine, isocarboxazid, and tranylcypromine) are of clinical interest. Clinicians must recognize that these drugs not only inhibit MAO but also exert other actions that may be clinically relevant. Thus, these compounds can block MAO uptake--tranylcypromine more than isocarboxazid or phenelzine. In addition, because tranylcypromine is structurally similar to amphetamine, it is believed to exert stimulant-like actions in the brain. Many issues are common to all three of these MAOIs.

Irreversible MAOIs

Indications and Efficacy

As discussed in the following subsections, irreversible MAOIs have been found to be effective in treating a variety of psychiatric disorders (Table 10-2).

TABLE 10-2. Indications for use of irreversible monoamine oxidase inhibitors (MAOIs)

Definitely effective	**Other possible uses**
Depressive disorder with atypical features	OCD
Major depressive disorder	Narcolepsy
Persistent depressive disorder	Headache
Depressive disorder with melancholic features	Chronic pain syndrome
Panic disorder	Generalized anxiety disorder

[a] Selegiline is the only MAOI that is useful in the treatment of Parkinson's disease.

Definitely effective	Other possible uses
PTSD	Premenstrual dysphoric disorder
Bulimia nervosa	
Atypical facial pain	
Anergic depression	
Treatment-resistant depression	
Parkinson's disease[a]	

[a] Selegiline is the only MAOI that is useful in the treatment of Parkinson's disease.

Major Depressive Disorder and Depressive Disorder With Atypical Features

Many studies have examined the efficacy of the irreversible MAOIs in the treatment of different types of depression. MAOIs have been effective in the treatment of major depressive disorder and atypical depression (defined as depression with anxiety or chronic pain, reversed vegetative symptoms, and rejection sensitivity [Quitkin *et al.* 1990]) (Davidson *et al.* 1987a; Himmelhoch *et al.* 1982, 1991; Johnstone 1975; Johnstone and Marsh 1973; McGrath *et al.* 1986; Paykel *et al.* 1982; Quitkin *et al.* 1979, 1990, 1991; Rowan *et al.* 1981; Thase *et al.* 1992; Vallejo *et al.* 1987; White *et al.* 1984; Zisook *et al.* 1985). Although early studies of relatively low-dosage regimens suggested that the efficacy of MAOIs was lower than that of TCAs, more recent studies have documented that their efficacy is comparable.

Quitkin *et al.* (1979, 1991) reviewed both phenelzine and tranylcypromine studies in patients with either atypical depression or melancholic depression. The authors reported that phenelzine appeared to be effective for the treatment of atypical depression.

Relatively few studies have investigated MAOIs in patients with endogenous depression (i.e., depression without known precipitating factors). From the limited number of patient studies, it is difficult to conclude that phenelzine is effective in the treatment of these patients. In addition, very few well-controlled studies have compared tranylcypromine with placebo. Three of the four studies that compared tranylcypromine with placebo showed that tranylcypromine was more effective (Himmelhoch *et al.* 1982; Moises and Beckmann 1981; White *et al.* 1984). In one study, a nonsignificant trend was found that favored tranylcypromine (Nolen 1989). Studies have also documented tranylcypromine's efficacy in treating anergic depression and, at high dosages, treatment-resistant depression (Himmelhoch *et al.* 1982, 1991; Thase *et al.* 1992; White *et al.* 1984). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, patients who had failed to respond to at least three treatment options were randomly assigned to receive tranylcypromine or a combination of extended-release venlafaxine and mirtazapine. Remission rates were modest for both the tranylcypromine group and the extended-release venlafaxine plus mirtazapine group, and the rates were not statistically different between groups (McGrath *et al.* 2006).

The heterogeneity of acetylation rates may account for some of the variance in response to phenelzine (Johnstone 1975; Johnstone and Marsh 1973; Paykel *et al.* 1982; Rowan *et al.* 1981). Approximately one-half of patients in a given population are slow acetylators. An initial study by Johnstone and Marsh (1973) suggested that slow acetylators improve more with phenelzine than do fast acetylators. Other researchers have been unable to confirm a relation between acetylation, acetylator type, and response to MAOIs.

Early studies suggested that irreversible MAOIs are particularly effective in patients with atypical depression. The concept of atypical depression remains controversial and has not been completely validated. The best differentiating criterion appears to be that phenelzine and other irreversible MAOIs are more effective than TCAs in treating patients with atypical depression (Cesura and Pletscher 1992; Quitkin *et al.* 1990; Zisook *et al.* 1985). A meta-review noted evidence that MAOIs are superior to TCAs, but not to SSRIs, in treating atypical depression (Cipriani *et al.* 2007).

Some studies have also suggested that MAOIs are effective in treating major depressive disorder and depression with melancholic features (Davidson *et al.* 1987a; McGrath *et al.* 1986; Vallejo *et al.* 1987). In a Cochrane Review, Lima and Moncrieff (2000) noted that MAOIs were comparable in efficacy to other classes of antidepressants in treating DSM-IV dysthymic disorder.

Panic Disorder

Both single-and double-blind studies have demonstrated the efficacy of phenelzine and iproniazid in treating panic disorder (Lydiard *et al.* 1989; Quitkin *et al.* 1990; Tyrer *et al.* 1973). About 50%-60% of patients with panic disorder respond to irreversible MAOIs. In the early stages of treatment, patients may have a worsening of symptoms. This is reduced in clinical practice by combining the MAOI with a benzodiazepine for the initial phase of treatment. It has been suggested that in addition to having an antipanic effect, phenelzine has an antiphobic action (Kelly *et al.* 1971). The time course of effect and the dosage used are similar to those for major depressive disorder.

Social Anxiety Disorder

Liebowitz *et al.* (1992) reported that phenelzine was effective in treating DSM-III (American Psychiatric Association 1980) social phobia. In an open-label study, Versiani *et al.* (1988) suggested that tranylcypromine was effective in treating this disorder as well. Versiani *et al.* (1992) also demonstrated the efficacy of the reversible MAOI moclobemide in a double-blind study. About 50% of patients responded to MAOIs, and the onset of response was gradual (usually about 2-3 weeks) (Liebowitz *et al.* 1992).

A Cochrane Review of pharmacotherapy for DSM-IV (American Psychiatric Association 1994) social phobia noted that whereas classic irreversible MAOIs were comparable in efficacy to SSRIs, reversible MAOIs were less efficacious (Stein *et al.* 2004).

Obsessive-Compulsive Disorder

Although initial case reports suggested that irreversible MAOIs may be effective in treating OCD (Jenike 1981), no double-blind studies conducted have indicated efficacy (Jenike *et al.* 1997).

Posttraumatic Stress Disorder

The classic MAOI phenelzine has been proven effective for the treatment of PTSD in single-blind trials (Davidson *et al.* 1987b) and in a double-blind crossover trial (Kosten *et al.* 1991).

Generalized Anxiety Disorder

MAOIs are not typically used to treat generalized anxiety disorder because the risk-benefit ratio favors the use of SSRIs, azapirones, or benzodiazepines. When they are used, MAOIs are selected primarily for treating treatment-resistant generalized anxiety disorder.

Bulimia Nervosa

Both phenelzine and isocarboxazid have been shown to be effective in treating some symptoms of bulimia nervosa (Kennedy *et al.* 1988; McElroy *et al.* 1989; Walsh *et al.* 1985, 1987).

Premenstrual Dysphoric Disorder

Preliminary studies and clinical experience have suggested that MAOIs may be effective in the treatment of premenstrual dysphoria (Glick *et al.* 1991).

Chronic Pain

MAOIs are believed to be effective in the treatment of atypical facial pain and other chronic pain syndromes. However, only limited data on these conditions are available.

Neurocognitive Disorders

The classic MAOIs have not been found to be effective for treating neurocognitive disorders such as Parkinson's disease and Alzheimer's disease. However, the MAO-B inhibitor selegiline has been shown to be effective in slowing the progression of Parkinson's disease (Cesura and Pletscher 1992), and two newer MAO-B inhibitors, rasagiline (TEVA Neuroscience 2014) and safinamide (U.S. WorldMeds 2017), are now approved for the treatment of Parkinson's disease (Dezsi and Vecsei 2017).

Side Effects and Toxicology

The side effects of irreversible MAOIs are generally not more severe or frequent than those of other antidepressants (Zisook 1984). The most frequent side effects are dizziness, headache, dry mouth, insomnia, constipation, blurred vision, nausea, peripheral edema, forgetfulness, fainting spells, trauma, urinary hesitancy, weakness, and myoclonic jerks. Loss of weight and appetite may occur with isocarboxazid use (Davidson and Turnbull 1982). Hepatotoxicity is rare with the currently available irreversible MAOIs, unlike with iproniazid. However, liver enzymes, such as aspartate transaminase and alanine transaminase, are elevated in 3%-5% of patients. Liver function tests must be done when patients have symptoms such as malaise, jaundice, and excessive fatigue.

Some side effects of irreversible MAOIs first emerge during maintenance treatment (Evans *et al.* 1982). These side effects include weight gain (which occurs in almost one-half of patients), edema, muscle cramps, carbohydrate craving, sexual dysfunction (usually anorgasmia), pyridoxine deficiency (Goodheart *et al.* 1991), hypoglycemia, hypomania, urinary retention, and disorientation. Peripheral neuropathy (Goodheart *et al.* 1991) and speech blockage (Goldstein and Goldberg 1986) are rare side effects of irreversible MAOIs. Weight gain is more of a problem with hydrazine compounds, such as phenelzine, than with tranylcypromine. Therefore, weight gain that is caused by hydrazine derivatives is an indication to switch to tranylcypromine. Edema is also more common with phenelzine than with tranylcypromine.

The management of some of these side effects can be difficult. Orthostatic hypotension is common with irreversible MAOIs. Addition of salt and salt-retaining steroids such as fludrocortisone (9-a-fluorohydrocortisone) is sometimes effective in treating orthostatic hypotension. Elastic support stockings are also helpful. Small amounts of coffee or tea taken during the day also keep the blood pressure elevated. The dose of fluorohydrocortisone should be adjusted carefully, because in elderly patients it could provoke cardiac failure resulting from fluid retention.

Sexual dysfunction that occurs with irreversible MAOIs is also difficult to treat. Common problems include anorgasmia, decreased libido, impotence, and delayed ejaculation (Harrison *et al.* 1985; Jacobson 1987). Cyproheptadine is sometimes effective in treating sexual dysfunction such as anorgasmia. Bethanechol may also be effective in some patients.

Insomnia occasionally occurs as an intermediate or late side effect of irreversible MAOIs. Changing the time of administration does not seem to help much, although dosage reduction may be helpful. Adding trazodone at bedtime is effective, but this should be done with caution. Myoclonic jerks, peripheral neuropathy, and paresthesias, when present, are also difficult to treat. When a patient has paresthesia, the clinician should evaluate for peripheral neuropathy and pyridoxine deficiency. In general, patients taking irreversible MAOIs should also receive concomitant pyridoxine therapy. When myoclonic jerks occur, patients can be treated with cyproheptadine.

Irreversible MAOIs also have the potential to suppress anginal pain; therefore, coronary artery disease could be overlooked or underestimated.

Patients with hyperthyroidism are more sensitive to irreversible MAOIs because of their overall sensitivity to pressor amines. Irreversible MAOIs can also worsen hypoglycemia in patients taking hypoglycemic agents such as insulin.

Dietary Interactions

After the introduction of irreversible MAOIs, several reports of severe headaches in patients who were taking these compounds were published ("Cheese and Tranylcypromine" 1970; Cronin 1965; Hedberg *et al.* 1966;

Simpson and Gratz 1992). These headaches were caused by a drug-food interaction. The risk of such an interaction is highest for tranylcypromine and lower for phenelzine, provided that the dosage of the latter remains low. However, the clinician must keep in mind that this interaction can occur even at low dosages with any of the classic MAOIs. The interaction of irreversible MAOIs with food has been attributed to increased tyramine levels. Tyramine, which has a pressor action, is present in a number of foods. It is normally broken down by the MAO enzymes and has both direct and indirect sympathomimetic actions. It has been suggested that the potentiation of tyramine by an MAOI may be secondary to increased release of norepinephrine rather than to the MAOI. Adrenaline would increase the indirect sympathetic activity of tyramine. The spontaneous occurrence of hypertensive crises in a few patients lends support to this hypothesis (O'Brien *et al.* 1992; Zajecka and Fawcett 1991).

The tyramine effect of food is potentiated by MAOIs 10-to 20-fold. A mild tyramine interaction occurs with about 6 mg of tyramine; 10 mg can produce a moderate episode, and 25 mg can produce a severe episode that is characterized by hypertension, occipital headache, palpitations, nausea, vomiting, apprehension, occasional chills, sweating, and restlessness. On examination, neck stiffness, pallor, mild pyrexia, dilated pupils, and motor agitation may be seen. The reaction usually develops within 20-60 minutes after ingestion of food. Occasionally, the reaction can be very severe and may lead to alteration of consciousness, hyperpyrexia, cerebral hemorrhage, and death. Death is exceedingly rare (Cooper 1989).

The classic treatment of the hypertensive reaction is phentolamine (5 mg) administered intravenously (Youdim *et al.* 1987; Zisook 1984). Nifedipine, a calcium channel blocker, has been shown to be effective (Stumpf 1988). Nifedipine has an onset of action of about 5 minutes, and it lasts approximately 3-5 hours; in fact, some clinicians have suggested that patients should carry nifedipine with them for immediate use in the event of a hypertensive crisis.

Because of the drug interaction of the classic MAOIs with food, clinicians usually make several dietary recommendations (Table 10-3). These recommendations are quite varied.

TABLE 10-3. **Food restrictions for monoamine oxidase inhibitors (MAOIs)**

To be avoided	To be used in moderation
Cheese (except cream cheese and cottage cheese)	Coffee
Overripe (aged) fruit (e.g., overripe bananas or avocados)	Chocolate
Fava beans	Colas
Sausage, salami	Tea
Beef and chicken livers	Soy sauce
Monosodium glutamate	Beer, other wines
Sauerkraut	
Pickled fish	
Brewer's yeast	
Fermented products	
Sherry, liqueurs	
Red wine	

MAOI diets recommend restriction of cheese (except cream cheese and cottage cheese), red wine, sherry, liqueurs, pickled fish, overripe (aged) fruit, brewer's yeast, fava beans, beef and chicken liver, and fermented products. Some diets recommend restriction of all alcoholic beverages, coffee, chocolate, colas, tea, yogurt, soy sauce, avocados, and bananas. Notably, many of the restricted foods--for example, avocados and bananas--rarely cause hypertensive crisis. For example, an interaction may occur only if overripe fruit is eaten or, in the case of bananas, if the skin is eaten (which is an uncommon practice in the United States). Similarly, unless a person ingests large amounts of caffeine, the interaction is usually not clinically significant. Although there is greater risk of noncompliance with highly restrictive diets, the clinician, when discussing restrictions and cautions with the patient, should emphasize the need to adhere to dietary restrictions and the potential risks that arise if they break the diet (Gardner *et al.* 1996).

Gillman's (2018) review of food science literature is a useful source to look for updated information on tyramine content of foods. High-tyramine foods can be encountered, but for the majority of people eating a regular diet, there are few foods that contain enough tyramine to provoke a major pressor response. But prudence is advised.

In evaluating patients who may have had a drug-food reaction, the clinician should evaluate the hypertensive reaction and differentiate it from histamine headache, which also can occur with an MAOI. Histamine headaches are usually accompanied by hypotension, colic, loose stools, salivation, and lacrimation (Cooper 1967). The clinician should provide both oral and printed instructions about food and drug interactions to patients who are taking classic MAOIs.

Norepinephrine reuptake inhibitors (e.g., reboxetine, desipramine, protriptyline, nortriptyline) are known to reduce the pressor response to tyramine (Dostert *et al.* 1997).

Drug-Drug Interactions

Drug-drug interactions are also extremely important concerns in patients taking irreversible MAOIs. The extensive inhibition of MAO enzymes by MAOIs increases the potential for a number of interactions with other drugs (Table 10-4). Of particular importance, many over-the-counter medications can interact with MAOIs. These medications include cough syrups containing sympathomimetic agents, which in the presence of an MAOI can precipitate a hypertensive crisis.

TABLE 10-4. Drug interactions with monoamine oxidase inhibitors (MAOIs)

Drug	Interaction	Comment
Other MAOIs (e.g., furazolidone, pargyline, procarbazine)	Potentiation of side effects; convulsions possible	Allow at least 1 week before changing to another MAOI
Tricyclic antidepressants (TCAs) (e.g., maprotiline, bupropion)	Possibility of severe side effects, such as hypertension and convulsions; serotonin syndrome	Allow at least 2 weeks before changing to an MAOI; combinations have been used occasionally for refractory depression
Carbamazepine	Low possibility of interaction; similar to TCAs	Same as for TCAs
Cyclobenzaprine	Low possibility of interaction; similar to TCAs	Same as for TCAs
Selective serotonin reuptake inhibitors (SSRIs)	Serotonin syndrome	Avoid combinations; allow at least 2 weeks before changing to an MAOI and 5 weeks if switching from fluoxetine to an MAOI
Stimulants (e.g., methylphenidate, dextroamphetamine)	Potential for increased blood pressure (hypertension)	Avoid combination
Buspirone	Potential for increased blood pressure (hypertension)	Avoid use; if used, monitor blood pressure
Meperidine	Possibility of severe, potentially fatal interaction (see	Avoid combination

Drug	**Interaction**	**Comment**
	text); serotonin syndrome	
Dextromethorphan	Reports of brief psychosis; possible serotonin syndrome	Avoid high dosages
Direct sympathomimetics (e.g., L-dopa)	Increased blood pressure	Avoid use if possible; if they need to be used, use with caution
Indirect sympathomimetics (e.g., ephedrine)	Hypertensive crisis possible	Avoid use
Oral hypoglycemics (e.g., insulin)	Worsening of hypoglycemia possible	Monitor blood sugar levels and adjust medications
Fenfluramine	Serotonin syndrome possible	Avoid use
L-Tryptophan	Serotonin syndrome possible	Avoid use

More detailed lists are available (Gillman 1998). Another area of caution is the use of MAOIs in patients who need surgery. Potential interactions include those with narcotic drugs, especially meperidine. Meperidine administered with MAOIs can produce a syndrome characterized by coma, hyperpyrexia, and hypertension. This syndrome has been reported primarily with phenelzine; however, it has also been reported with tranylcypromine (Mendelson 1979; Stack *et al.* 1988). Stack *et al.* (1988) noted that this syndrome is most likely to occur with meperidine and that it may be related to that drug's serotonergic properties (similar to serotonin syndrome). Similar reactions have not been reported to any significant extent with other narcotic analgesics such as morphine and codeine. In fact, many patients probably receive these medications without problems. Only a small fraction of patients may have this interaction, and it could reflect a serotonin toxicity effect. In general, current opinion favors the use of morphine when intra-or postoperative narcotics are needed in patients taking MAOIs.

The issue of whether directly acting sympathomimetic amines interact with MAOIs is more controversial. Intravenous administration of sympathomimetic amines to patients receiving MAOIs does not provoke hypertension. When a bolus infusion of any of various catecholamines is given to healthy volunteer subjects who have been taking phenelzine or tranylcypromine for 1 week, a potentiation of the pressor effect of phenylephrine occurs, but no clinically significant potentiation of cardiovascular effects of norepinephrine, epinephrine, or isoproterenol occurs (Wells and Bjorksten 1989).

In general, direct sympathomimetic amine-MAOI interactions do not appear to produce significant cardiovascular problems. However, there is a low incidence of hypertensive episodes in the presence of indirect sympathomimetics. Ideally, these compounds should not be used in patients who are receiving MAOIs. A direct-acting compound is preferable to an indirect-acting compound.

Caution should be exercised when using MAOIs in patients with pheochromocytoma or with cardiovascular, cerebrovascular, or hepatic disease. Because phenelzine tablets contain gluten, they should not be given to patients with celiac disease.

Each patient should be given a card indicating that he or she is taking an MAOI and instructed to carry the card at all times. A medical bracelet indicating that the wearer takes an MAOI is also a good idea.

Specific Monoamine Oxidase Inhibitors

Phenelzine

Phenelzine, a hydrazine derivative, is a potent irreversible MAOI and is the best studied of the MAOIs.

Pharmacokinetics

Phenelzine is a substrate as well as an inhibitor of MAO. Major identified metabolites of phenelzine include phenylacetic acid and *p*-hydroxyphenylacetic acid. Phenelzine undergoes acetylation, and therefore drug levels are lower in fast acetylators than in slow acetylators. However, because phenelzine is an irreversible inhibitor, plasma concentrations are not relevant. The antidepressant effect, the degree of inhibition of MAO, and the amount of free phenelzine excreted in the urine are all significantly greater in slow acetylators than in fast acetylators (Baker *et al.* 1999).

Indications

Phenelzine is useful in the treatment of major depressive disorder, atypical depression, panic disorder, social phobia, and atypical facial pain (see section "Indications and Efficacy" earlier in this chapter).

Side Effects

The primary side effects of phenelzine are similar to those of other MAOIs. Hepatitis secondary to phenelzine may occur in rare cases (< 1 in 30,000). The most difficult side effect, often leading to discontinuation, is postural hypotension.

Contraindications

The contraindications to phenelzine include known sensitivity to the drug, pheochromocytoma, congestive heart failure, and history of liver disease. (In addition, see sections "Dietary Interactions" and "Drug-Drug Interactions" earlier in this chapter.)

Isocarboxazid

Isocarboxazid is an irreversible MAOI of the hydrazine type.

Pharmacokinetics

Isocarboxazid is rapidly absorbed from the gastrointestinal tract and is metabolized in the liver. It is primarily excreted as hippuric acid. Its half-life is of little interest because it is an irreversible MAOI. Chemically, isocarboxazid is 5-methyl-3-isoxazolecarboxylic acid 2-benzylhydrazide. Isocarboxazid is a colorless crystalline substance with very little taste.

Indications

Isocarboxazid is the least studied of the MAOIs. It is indicated for the treatment of depression.

Side Effects

The side effects of isocarboxazid are similar to those of phenelzine, described earlier in this section. Postural hypotension is the most common problem.

Contraindications

The contraindications to isocarboxazid are similar to those of phenelzine, described earlier in this section.

Tranylcypromine

Tranylcypromine, a nonhydrazine irreversible MAOI, increases the concentration of norepinephrine, epinephrine, and 5-HT in the CNS. Tranylcypromine has a mild stimulant effect.

Pharmacokinetics

Limited data exist on the pharmacokinetics of tranylcypromine. The drug is excreted within 24 hours. The dynamic effect lasts for up to 5 days after withdrawal. There is considerable debate about whether tranylcypromine is metabolized to amphetamine; most studies in the literature indicate that this does not occur.

Indications

Tranylcypromine is indicated for the treatment of major depressive disorder without melancholia.

Side Effects

The side effects of tranylcypromine are similar to those of other MAOIs. In addition, problems with physical dependence on tranylcypromine have been reported. Thus, withdrawal symptoms, such as anxiety, restlessness, depression, and headache, may occur. Syndrome of inappropriate antidiuretic hormone (SIADH) has been reported with tranylcypromine. Rare cases of toxic hepatitis have also been reported. Tranylcypromine can lead to increased agitation, insomnia, and restlessness compared with phenelzine.

Contraindications

The contraindications to tranylcypromine are the same as those for phenelzine, described earlier in this section. In addition, in view of the greater potential for hypertensive episodes, tranylcypromine should be used with particular caution in patients with cerebrovascular or cardiovascular disease.

Moclobemide

Moclobemide, a reversible inhibitor of MAO-A enzyme (Amrein *et al.* 1989), has a higher potency in vivo than in vitro. Therefore, it has been suggested that moclobemide is a prodrug and that it is metabolized to a form with higher affinity for MAO-A than the parent compound. After single-or repeated-dose administration of moclobemide, the recovery of MAO-A activity is much quicker than that seen with other MAOIs. One of the metabolites of moclobemide does inhibit MAO-B; however, this action is minimally significant in humans. When administered to rats, moclobemide increases the concentration of 5-HT, norepinephrine, epinephrine, and dopamine in rat brain (Haefely *et al.* 1992). These effects are short-lasting, and they parallel the time course of MAO-A inhibition. In addition, unlike with irreversible inhibitors, repeated administration does not increase the inhibition.

Moclobemide only partially potentiates the blood pressor effect of oral tyramine (Da Prada *et al.* 1989). This is because it is a reversible inhibitor with a low affinity for the MAO isoenzymes and is easily displaced by the pressor amines ingested in food. On the basis of these studies, moclobemide is thought to be safer than irreversible MAOIs.

Pharmacokinetics

After oral administration of moclobemide, peak plasma concentrations are reached within 1 hour. The drug is about 50% bound to plasma proteins and is extensively metabolized; only 1% of the compound is excreted (unchanged) in the urine. The half-life of the compound is approximately 12 hours. Moclobemide is extensively metabolized; 95% of the administered dosage is excreted in the urine. The metabolites are pharmacologically inactive. The presence of food reduces the rate (but not the extent) of moclobemide absorption.

Indications

Moclobemide has been studied in all types of depressive disorders (Gabelic and Kuhn 1990; Larsen *et al.* 1991; Rossel and Moll 1990). Controlled trials have found that it is superior to placebo. In addition, moclobemide has been found to be as effective as

imipramine, desipramine, clomipramine, and amitriptyline in the treatment of depression. The dosage required is 300-600 mg/day.

Unlike the classic MAOIs, moclobemide has been found to be effective in treating both endogenous and nonendogenous depression. In addition, in combination with antipsychotics, the drug seems to be effective in treating psychotic depression (Amrein *et al.* 1989). Moclobemide has also been effective in treating bipolar endogenous depression.

Versiani *et al.* (1992) compared phenelzine, moclobemide, and placebo and reported that both phenelzine and moclobemide were superior to placebo in treating patients with social phobia. Given the efficacy of classic MAOIs in the treatment of other psychiatric disorders, such as bulimia, panic disorder, and PTSD, it is likely that patients with such disorders would also respond to a reversible MAOI. Additional trials of moclobemide are required to confirm its utility in other psychiatric disorders.

Side Effects

Nausea was the only side effect noted to be greater in patients taking moclobemide than in patients taking placebo. Thus, the profile of moclobemide seems to be ideal in that it causes few or no major side effects. Case reports have shown no toxicity after overdoses of up to 20 g (Amrein *et al.* 1989).

Dietary Interactions

Intravenous tyramine pressor tests indicate that a single dose of moclobemide increases tyramine sensitivity (Cusson *et al.* 1991). However, this increase is small compared with the increase associated with other MAOIs. Under most conditions, there appears to be limited drug-food interaction. However, to minimize even mild tyramine pressor effects, the recommended action is to administer moclobemide after a meal rather than before it. In a study in which tyramine was administered in doses up to 100 mg, inpatients pretreated with moclobemide had no significant changes in blood pressure. The drug also has minimal effect on cognitive performance and no effect on body weight or hematological parameters (Wesnes *et al.* 1989; Youdim *et al.* 1987).

Drug-Drug Interactions

Several studies have examined potential drug-drug interactions with moclobemide (Amrein *et al.* 1992). No drug interaction with lithium has been reported. No interactions with benzodiazepines or antipsychotics have been reported (Amrein *et al.* 1992). Parallel data suggest that moclobemide can potentiate the effects of meperidine; therefore, a narcotic-MAOI interaction may occur. Combination with other antidepressants (including SSRIs) is best avoided in view of potential serotonin toxicity. Until proven otherwise, it would be prudent to avoid the combination of moclobemide with opiates like meperidine and other drugs that can increase serotonin. A pharmacokinetic interaction has been observed with cimetidine that requires the reduction of the moclobemide dose because cimetidine reduces the clearance of moclobemide.

Selegiline Hydrochloride

Selegiline hydrochloride is an irreversible MAO-B inhibitor (Cesura and Pletscher 1992). Its primary use is in the treatment of Parkinson's disease, as an adjunct to L-dopa

and carbidopa. The average dosage for Parkinson's disease is 5-10 mg/day. The exact mechanism of action of MAO-B in Parkinson's disease is unknown (Gerlach *et al.* 1996; Hagan *et al.* 1997; Lyytinen *et al.* 1997). In the United States, selegiline dosage forms include tablets, capsules, orally disintegrating tablets, and extended-release transdermal patches (see next section, "Selegiline Transdermal System").

Pharmacokinetics

Selegiline is metabolized to levoamphetamine, methamphetamine, and *N*-desmethylselegiline. Selegiline hydrochloride undergoes significant first-pass metabolism following oral administration. Transdermal delivery avoids the first-pass effect and provides greater levels of unchanged drug and reduced levels of metabolites compared with the oral regimen. The time to reach the peak plasma concentration is less than 1 hour. The elimination half-life of selegiline is about 1.5 hours. There is at least a threefold increase in the area under the curve (AUC) of selegiline with food (Mahmood 1997).

Indications and Efficacy

The efficacy of oral selegiline in treating depression has not been well studied. Quitkin *et al.* (1984) showed that selegiline was superior to placebo administered to patients with depression in a 6-week double-blind study. Dosages of more than 10-20 mg/day were needed. The dosage required for treating depression may be much higher than that required to treat Parkinson's disease. At higher dosages, dietary interactions could occur. Early studies also found that selegiline is of modest benefit in patients with Alzheimer's disease (Lawlor *et al.* 1997).

Side Effects

The few side effects that have been noted with selegiline include nausea, dizziness, and light-headedness. When the drug is abruptly discontinued, nausea, hallucinations, and confusion have been reported.

Dietary Interactions

Because MAO-B is not involved in the intestinal tyramine interaction, dietary interaction with selegiline (at low dosages of 5-10 mg/day) would probably be minimal. An interaction between selegiline and narcotics has been reported and should be kept in mind.

Drug-Drug Interactions

Selegiline's potential drug interactions are similar to those of other MAOIs, and there is a risk for serotonin syndrome if selegiline is combined with other drugs (including SSRIs) that can increase serotonin.

Selegiline Transdermal System

The selegiline transdermal system (STS) was developed to overcome limitations of orally administered MAOIs, particularly dietary tyramine restrictions. STS does not overcome drug-drug interactions. It bypasses the gut, thereby reducing drug-food interactions. The pharmacokinetic and pharmacodynamic properties promote the inhibition of MAO-A and MAO-B in the CNS while avoiding significant inhibition of intestinal and liver MAO-A enzymes. Three different strengths of the STS patch are currently marketed: 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2. The three patch sizes deliver 24-hour doses of selegiline averaging 6 mg, 9 mg, and 12 mg, respectively. Use of the 6-mg patch does not call for dietary modification. A restricted "MAOI diet" is advised for the higher-dosage 9-mg and 12-mg patches to avoid any risk of hypertensive crisis. Patients are strongly advised to follow these restrictions.

Pharmacokinetics

Following dermal application of the STS patch, 25%-30% of the selegiline content on average is delivered systemically over 24 hours. Consequently, the degree of drug absorption is one-third higher than the average amounts of 6-12 mg/24 hours. In comparison with oral dosing, transdermal dosing results in substantially higher exposure to selegiline and lower exposure to metabolites.

Indications and Efficacy

The efficacy of STS as a treatment for major depressive disorder was established in two placebo-controlled studies of 6 and 8 weeks' duration in adult outpatients with major depressive disorder. In both studies, patients were randomly assigned to receive double-blind treatment with drug patch or placebo. The 6-week trial showed that 6 mg/24 hours was significantly more effective than placebo, as assessed by scores on the 17-item Hamilton Rating Scale for Depression (Ham-D) (Amsterdam 2003). In an 8-week dosage titration trial, depressed patients receiving the drug patch (starting dosage was 6 mg/24 hours, with possible increases to 9 mg/24 hours or 12 mg/24 hours based on clinical response) showed significant improvement compared with those receiving placebo on the primary outcome measure, the 28-item Ham-D total score (Feiger *et al.* 2006). In another trial, 322 patients with symptoms meeting DSM-IV-TR (American Psychiatric Association 2000) criteria for major depressive disorder who had responded during an initial 10-week open-label treatment phase were randomly assigned either to continuation at the same dosage or to placebo under double-blind conditions for observation of relapse. In this double-blind phase, patients receiving continued STS experienced a significantly longer time to relapse (Amsterdam and Bodkin 2006). The efficacy of STS was also studied in a double-blind study of adolescents with depression. There was no significant difference between patients receiving STS and those receiving placebo (DelBello *et al.* 2014).

Side Effects

The main side effects with STS are diarrhea, application site reactions (e.g., skin irritation, rash), and insomnia.

Drug-Drug Interactions

Potential drug-drug interactions for STS are the same as for other MAOIs.

Conclusion

Various MAOIs have been shown to be effective in treating a wide variety of psychiatric disorders, including depression, panic disorder, social phobia, and PTSD. The classic

MAOIs are currently used only rarely as first-line medication because of potential dietary interactions and other long-term side effects. The reversible inhibitors of MAO-A enzyme, such as moclobemide, which have fewer side effects and no dietary restrictions compared with classic MAOIs, are unlikely to be introduced in the United States. In fact, the risk-benefit ratio for these compounds is highly favorable compared with other antidepressants. The MAO-B inhibitor selegiline is used to reduce the progression of Parkinson's disease. Its utility in treating other degenerative disorders is currently being assessed. STS reduces dietary interactions when used at low dosages and is now approved for the treatment of major depressive disorder. New applications and a wider use of these compounds may be found in the near future.

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Tricyclic and Tetracyclic Drugs

J. Craig Nelson, M.D.

The tricyclic antidepressants hold an important place in the history of treatments for depression. They were the first class of antidepressant compounds to be widely used for depression and remained the first-line treatment for more than 30 years. Observations of their activity led to theories of drug action involving norepinephrine and serotonin. Indeed, this "psychopharmacological bridge" suggested that alterations of these neurotransmitters might cause depression (Bunney and Davis 1965; Prange 1964; Schildkraut 1965). As a result of extensive research on the tricyclics, the field developed several key principles to guide the management of depressive illness. For example, clinicians recognized the importance of not only providing an adequate medication dosage and duration during acute treatment but also sustaining symptom improvements during continuation. Adverse events associated with the tricyclics required that psychiatrists become familiar with a variety of syndromes such as anticholinergic delirium, delayed cardiac conduction, and orthostatic hypotension. The observation that tricyclic plasma concentrations varied widely stimulated interest in the relationship of these drug concentrations to hepatic metabolism and clinical activity. The field was introduced to the concepts of genetic polymorphisms in the cytochrome P450 (CYP) enzyme system. Finally, knowledge of how these drugs work became the basis for the discovery of new drugs such as the selective serotonin reuptake inhibitors (SSRIs).

History and Discovery

In 1957, the Swiss psychiatrist Roland Kuhn investigated the clinical effects of imipramine, in part to determine whether its sedative properties might be useful for humans (Kuhn 1958, 1970). He found that although imipramine was not useful in

calming agitated patients, it ameliorated symptoms in patients with depression. After imipramine was introduced, several other antidepressant compounds were developed and marketed.

Structure-Activity Relations

Tricyclic and tetracyclic compounds are categorized based on their chemical structure (Figure 11-1). The tricyclics have a central three-ring structure--hence the name. The tertiary-amine tricyclics, such as amitriptyline and imipramine, have two methyl groups at the end of the side chain. These compounds can be demethylated to secondary amines such as desipramine and nortriptyline. The tetracyclic compound maprotiline has a four-ring central structure. Five tertiary amines have been marketed in the United

States: amitriptyline, clomipramine, doxepin, imipramine, and trimipramine. The three secondary-amine compounds are desipramine, nortriptyline, and protriptyline. All of these compounds, in addition to amoxapine and maprotiline, have been approved for use in major depressive disorder with the exception of clomipramine, which is approved for use only in OCD in the United States.

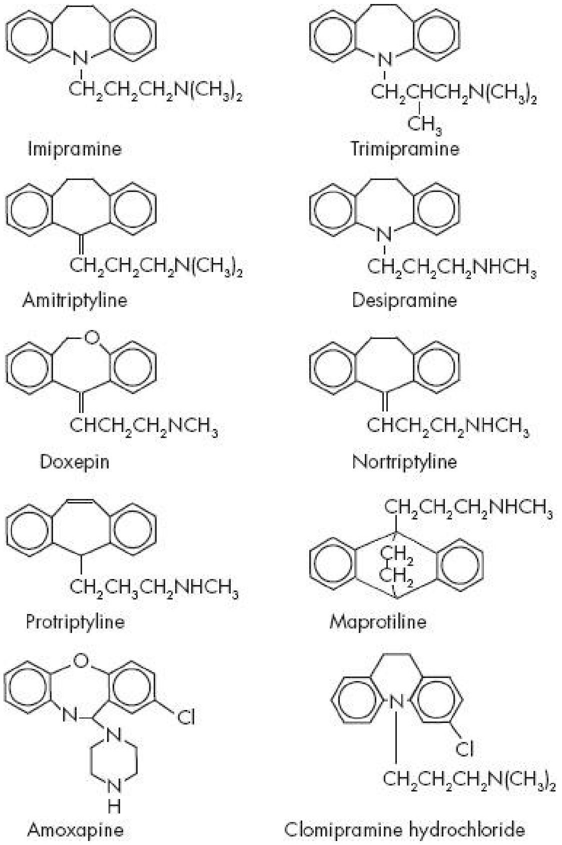
N
$CH_2CH_2CH_2N(CH_3)_2$
Imipramine
N
$CH_2CHCH_2N(CH_3)_2$
CH_3
Trimipramine
$CH_2CH_2CH_2N(CH_3)_2$
Amitriptyline
N
$CH_2CH_2CH_2NHCH_3$
Desipramine
O
$CHCH_2CH_2NCH_3$
Doxepin
$CHCH_2CH_2NHCH_3$
Nortriptyline
$CH_2CH_3CH_2NHCH_3$
Protriptyline
$CH_2CH_2CH_2NHCH_3$
CH_2
CH_2
Maprotiline
O
N
N
N
H
Cl
Amoxapine
N
Cl
$CH_2CH_2CH_2N(CH_3)_2$
Clomipramine hydrochloride

FIGURE 11-1. Chemical structures of the tricyclic and tetracyclic antidepressants.

The structure of the side chain is important for the function of tricyclic antidepressants. The tertiary tricyclic agents--amitriptyline, imipramine, and clomipramine--are more potent in blocking the serotonin transporter. The secondary tricyclics are much more potent in blocking the norepinephrine transporter (Table 11-1) (Bolden-Watson and Richelson 1993; Tatsumi *et al.* 1997).

TABLE 11-1. Affinity of tricyclic and tetracyclic antidepressants for neurotransmitter transporters and specific receptors

	Potency uptake blockade			**Receptor binding affinity**					
Drug	**5-HT**	**NE**	**DA**	a_1	a_2	H_1	M_1	**5-HT**$_{1A}$	**5-HT**$_2$
Amitriptyline	4.3	35.0	3,250	27	940	1.1	18	450	18
Amoxapine	58.0	16.0	4,310	50	2,600	25	1,000	220	1
Clomipramine	0.28	38.0	2,190	38	3,200	31	37	7,000	27

Note. Values are expressed as equilibrium dissociation constants. a_1 = a_1-adrenergic; a_2 = a_2-adrenergic; DA = dopamine; 5-HT = serotonin; 5-HT$_{1A}$ = serotonin$_{1A}$; 5-HT$_2$ = serotonin 2; H_1 = histamine 1; M_1 = muscarinic 1; NE = norepinephrine.

Source. Potency uptake data adapted from Tatsumi *et al.* 1997. Receptor affinity data adapted from Richelson and Nelson 1984.

	Potency uptake blockade			Receptor binding affinity					
Drug	**5-HT**	**NE**	**DA**	a_1	a_2	H_1	M_1	**5-HT**$_{1A}$	**5-HT**$_2$
Desipramine	17.6	0.83	3,190	130	7,200	110	198	6,400	350
Doxepin	68.0	29.5	12,100	24	1,100	0.24	80	276	27
Imipramine	1.4	37.0	8,500	90	3,200	11	90	5,800	150
Maprotiline	5,800.0	11.1	1,000	90	9,400	2	570	12,000	120
Nortriptyline	18.0	4.37	1,140	60	2,500	10	150	294	41
Protriptyline	19.6	1.41	2,100	130	6,600	25	25	3,800	67
Trimipramine	149.0	2,450.0	3,780	24	680	0.27	58	8,400	32
Reference									
Pentolamine				15.0					
Yohimbine					1.6				
D-Chlorpheniramine						15.0			
Atropine							2.4		
Serotonin								0.72	
Ketanserin									2.5

Note. Values are expressed as equilibrium dissociation constants. a_1 = a_1-adrenergic; a_2 = a_2-adrenergic; DA = dopamine; 5-HT = serotonin; 5-HT$_{1A}$ = serotonin$_{1A}$; 5-HT$_2$ = serotonin 2; H_1 = histamine 1; M_1 = muscarinic 1; NE = norepinephrine.

Source. Potency uptake data adapted from Tatsumi *et al.* 1997. Receptor affinity data adapted from Richelson and Nelson 1984.

The structure of amoxapine differs from the structures of the other tricyclics. With a central three-ring structure and a side chain unlike those of the tricyclics, amoxapine is structurally closer to the antipsychotic loxapine, from which it is derived. Like the secondary tricyclics, amoxapine is a potent norepinephrine reuptake inhibitor. Unlike the other compounds in this group, amoxapine--particularly its metabolite 7-hydroxyamoxapine--blocks postsynaptic dopamine receptors (Coupet *et al.* 1979). As a result, it is the only compound in the group that has antipsychotic activity in addition to antidepressant effects.

Maprotiline also differs from the others in this group. Although maprotiline is tetracyclic, its side chain is identical to that in desipramine, nortriptyline, and protriptyline. As would be predicted from this similarity, maprotiline is most potent in blocking the norepinephrine transporter (Randrup and Braestrup 1977).

Pharmacological Profile

Reuptake Blockade

Early in the history of the tricyclic and tetracyclic antidepressants, the ability of these compounds to block the transporter site for norepinephrine was described (Axelrod *et al.* 1961) (see Table 11-1). The tertiary amines have greater affinity for the serotonin transporter, whereas the secondary amines are relatively more potent at the norepinephrine transporter. During administration of amitriptyline, imipramine, or clomipramine, these tertiary amines are demethylated to secondary amines; thus, both serotonergic and noradrenergic effects occur. In addition, because dopamine is inactivated by norepinephrine transporters in the frontal cortex (Bymaster *et al.* 2002), norepinephrine reuptake inhibitors would be expected to increase dopamine concentrations in that region.

The initial reuptake blockade is followed by a specific sequence of events (Blier *et al.* 1987; Charney *et al.* 1991; Tremblay and Blier 2006). After reuptake blockade, levels of serotonin and norepinephrine increase. As a result of inhibitory feedback from the presynaptic autoreceptors, the firing rate of the presynaptic neuron slows and concentrations of the major metabolites of serotonin and norepinephrine decrease rapidly. In the serotonin system, the presynaptic autoreceptor is desensitized over a 10-to 14-day period, and the tonic firing rate returns to its pretreatment rate. With both a normal firing rate and reuptake blockade, serotonin transmission is enhanced. In contrast, the firing rate of noradrenergic neurons remains inhibited with chronic treatment (Szabo and Blier 2001), suggesting that somatodendritic a_2-autoreceptors do not desensitize. Norepinephrine concentrations increase at postsynaptic sites such as the hippocampus and frontal cortex, which may indicate desensitization of terminal a_2-autoreceptors. With chronic treatment, the postsynaptic b-adrenergic receptor is downregulated or decreased in density (Sulser *et al.* 1978). Current evidence suggests that b-adrenergic receptor downregulation is likely a compensatory change. Overall, chronic administration of norepinephrine reuptake inhibitors results in enhanced noradrenergic transmission. This effect manifests as enhanced formation of second-messenger cyclic adenosine monophosphate (Duman *et al.* 1997) and is reflected clinically by a persistent increase in heart rate (Roose *et al.* 1998; Rosenstein and Nelson 1991).

The tricyclic agents also sensitize or upregulate postsynaptic serotonin_{1A} (5-HT_{1A}) receptors (de Montigny and Aghajanian 1978). These changes further enhance the effects of serotonin. In addition, tricyclics downregulate serotonin_2 (5-HT_2) receptors (Peroutka and Snyder 1980). In preclinical experiments, the effects of serotonin were enhanced when an antagonist blocked the 5-HT_2 receptor (Lakoski and Aghajanian 1985; Marek *et al.* 2003). Some tricyclics, particularly amoxapine and doxepin (and to some extent amitriptyline), have 5-HT_2 antagonist properties that are relatively comparable to their reuptake potency (see Table 11-1) (Tatsumi *et al.* 1997).

Secondary Effects

The tricyclic and tetracyclic compounds have a variety of additional actions mediated by other receptors (Cusack *et al.* 1994; Richelson and Nelson 1984) (see Table 11-1). For example, these compounds block muscarinic receptors, producing anticholinergic effects. Although these anticholinergic effects have generally been thought to mediate the adverse effects of the tricyclics and tetracyclics, a double-blind randomized crossover study of 19 individuals with major depressive disorder reported that the anticholinergic drug scopolamine had a beneficial effect on depressive and anxious symptoms (Furey and Drevets 2006). Consistent with this finding, the cholinesterase inhibitor donepezil increased the risk of depression relapse among older adults when given as an adjunct to an SSRI (Reynolds *et al.* 2011). Tricyclics also block histamine_1 (H_1) receptors and a_1- and a_2-adrenergic receptors, resulting in a variety of other effects (as discussed later in "Side Effects and Toxicology"). Tricyclics act on voltage-gated sodium channels, which explains their adverse cardiac effects; however, these same actions may contribute to the beneficial effects of these antidepressants on pain (Liang *et al.* 2014; Priest and

Kaczorowski 2007). The potency of secondary effects of tricyclics and tetracyclics varies considerably. Among the tricyclics, amitriptyline is the most anticholinergic and desipramine is the least. Doxepin is the most potent H_1 antagonist among the tricyclics, but mirtazapine is even more potent. The consequences of these secondary effects are discussed later in this chapter ("Side Effects and Toxicology").

Pharmacokinetics and Disposition

Absorption

Absorption of the tricyclic and tetracyclic drugs occurs in the small intestine and is rapid and reasonably complete. Peak levels are reached within 2-8 hours after ingestion, with the exception of protriptyline (6-12 hours) and maprotiline (8 hours or longer). Although peak levels may have implications for side effects, they are relatively unimportant with respect to efficacy because the antidepressant action of these drugs occurs over several weeks.

Volume of Distribution

The tricyclic and tetracyclic compounds are basic lipophilic amines and are concentrated in a variety of tissues throughout the body. As a result, they have a high volume of distribution. For example, concentrations of these drugs in cardiac tissue exceed concentrations in plasma.

Plasma Protein Binding

Tricyclic and tetracyclic antidepressants are extensively bound to plasma proteins (e.g., 90% or greater) because of their lipid solubility. Exceptions are the hydroxy metabolites, which have lower plasma protein binding than the parent compounds.

First-Pass Metabolism

After absorption, the tricyclics are taken up in the circulation but pass first through the liver, where metabolism of the drug begins. As a result, the amount of compound that enters the systemic circulation is reduced.

Hepatic Metabolism

Hepatic metabolism is the principal method of clearance for the tricyclic and tetracyclic compounds. Only a small portion of drug is eliminated by the kidneys. Rates of hepatic metabolism vary widely from person to person, resulting in dramatic differences in steady-state plasma concentrations. For example, in a sample of 83 white inpatients given a fixed dose of desipramine (2.5 mg/kg), steady-state plasma concentrations ranging from 20 to 934 ng/mL were observed (Nelson 1984). Elimination half-lives for most of the tricyclic and tetracyclic compounds average about 24 hours or longer; thus, these drugs can be given once per day (Table 11-2). Amoxapine has a shorter half-life than the other tricyclics and is an exception.

TABLE 11-2. Dosage, clearance, and apparent therapeutic plasma concentrations of tricyclic and tetracyclic antidepressants

	Plasma		Therapeutic	
Drug	Half-life (hours)	Clearance (L/hour)	Dosage range (mg/day)	Plasma level (ng/mL)
Tertiary tricyclics				
Amitriptyline	5-45	20-70	150-300	
Clomipramine	15-60	20-120	150-300	> 150[a]
Doxepin	10 -25	40-60	150-300	
Imipramine	5-30	30-100	150-300	> 200[a]
Trimipramine	15-40	40-105		
Secondary tricyclics				
Desipramine	10-30	80-170	75-300	> 125
Nortriptyline	20-55	15-80	50-150	50-150
Protriptyline	55-200	5-25	15-60	
Tetracyclics				
Amoxapine	5-10	225-275	150-300	
Maprotiline[b]	25-50	15-35	100-225	

[a] Total concentration of the parent compound and the desmethyl metabolite.

[b] According to the FDA Orange Book (U.S. Food and Drug Administration 2023), product availability may be limited from time to time.

Source. Adapted from Nelson JC: "Tricyclic and Tetracyclic Drugs," in *Comprehensive Textbook of Psychiatry/VII,* 7th Edition. Edited by Kaplan HI, Sadock BJ. Baltimore, MD, Lippincott Williams & Wilkins, 2000, p. 2494. Copyright 2000, Lippincott Williams & Wilkins. Used with permission.

Hepatic metabolism of the tricyclics and tetracyclics occurs along two principal pathways. In one pathway, *demethylation of the side chain* converts the tertiary amines to secondary amines and involves several CYP isoenzymes, including CYP1A2, CYP3A4, and CYP2C19. In the other pathway, *hydroxylation of the ring structure* is regulated by the CYP2D6 isoenzyme and produces hydroxy metabolites (Brosen *et al.* 1991). In some cases, the levels of the metabolite are substantial. The concentration of 10-hydroxynortriptyline usually exceeds that of the parent compound (Bertilsson *et al.* 1979). Usually 2-hydroxydesipramine is present at levels approximately 40%-50% of those of the parent compound, but these ratios are quite variable and depend on the hydroxylation rate (Bock *et al.* 1983; Potter *et al.* 1979). Hydroxynortriptyline and hydroxydesipramine both block the norepinephrine transporter (Bertilsson *et al.* 1979; Potter *et al.* 1979) and have antidepressant activity (Nelson *et al.* 1988b; Nordin *et al.* 1987). Hydroxyimipramine and hydroxyamitriptyline are present at very low concentrations and are clinically unimportant. The hydroxy metabolites are then conjugated and excreted. The conjugated metabolites are not active.

The principal metabolic pathway for amoxapine is hydroxylation, during which 7-hydroxyamoxapine and 8-hydroxyamoxapine are produced (Coupet *et al.* 1979). These compounds differ: whereas 7-hydroxyamoxapine has high-potency antipsychotic properties but a short half-life, 8-hydroxyamoxapine is metabolized more slowly and appears to contribute to the drug's antidepressant action.

The hepatic isoenzymes are under the control of specific genes, and gene loci for several of these isoenzymes, including CYP2D6, have been identified. Approximately 5%-10% of white individuals are homozygous for the recessive autosomal CYP2D6 trait, resulting in deficient hydroxylation of desipramine and nortriptyline (Brosen *et al.* 1985; Evans *et al.* 1980). Approximately 50% of individuals of Asian descent carry the *CYP2D6*10* allele, which is associated with intermediate metabolism of CYP2D6 substrates (Ji *et al.* 2002). For example, the elimination half-life of nortriptyline is doubled in individuals homozygous for this allele (Yue *et al.* 1998).

P-Glycoprotein and the Blood-Brain Barrier

P-glycoprotein (P-gp) is located at the blood-brain barrier and acts as an efflux pump. P-gp protects the organism from exogenous compounds. It is hypothesized that by limiting uptake of antidepressants into the CNS, P-gp contributes to medication resistance. Most tricyclics are substrates of P-gp (Akamine *et al.* 2012; O'Brien *et al.* 2012). The effectiveness of P-gp is reduced in the presence of P-gp inhibitors (e.g., verapamil and quinidine), and these agents would be expected to increase CNS concentrations of P-gp substrates (Weiss *et al.* 2003). However, the utility of adjunctive treatment with a P-gp inhibitor to improve outcomes has not been demonstrated.

P-gp is encoded by the gene *ABCB1*. Polymorphisms of *ABCB1* decrease the efficiency of P-gp and should result in higher CNS concentrations of P-gp substrates. Although an early study showed that remission with P-gp substrates was associated with *ABCB1* polymorphisms (Uhr *et al.* 2008), a review and meta-analysis of the association of *ABCB1* variants with outcomes reported considerable variability in the findings of 16 studies (Breitenstein *et al.* 2015). Furthermore, the investigators in the two largest studies included in the meta-analysis found that none of the *ABCB1* variants were associated with response to P-gp substrate antidepressants. These findings suggest limited applicability of genotype *ABCB1* as a predictor of response in depression.

Linear Kinetics

Most of the tricyclics have linear kinetics--that is, their concentration increases in proportion to dose within the therapeutic range. There are exceptions. Desipramine, for example, has nonlinear kinetics at the usual dosage range (Nelson and Jatlow 1987). In cases of overdose, pharmacokinetics are more likely to change from linear to nonlinear metabolism, and the clinician cannot assume that usual rates of drug elimination will be maintained.

Effects of Aging

Changes in the pharmacodynamics and pharmacokinetics of medications occur with aging, but they vary in importance (Greenblatt *et al.* 1998). The ratio of fat to lean body mass increases, and cardiac output and hepatic blood flow decrease. There may be further changes associated with medical illness, but their clinical importance is usually relatively minor because of the dramatic variability of hepatic metabolism. The activity of the CYP3A4 pathway slows with age (von Moltke *et al.* 1995), and concentrations of the tertiary amines are increased somewhat in older individuals (Abernethy *et al.* 1985). However, most studies of nortriptyline (Katz *et al.* 1989; Young *et al.* 1984) and desipramine (Abernethy *et al.* 1985; Nelson *et al.* 1985, 1995) indicate that the ratios of blood level to dosage are relatively unaffected by aging, suggesting that the CYP2D6 isoenzyme is not similarly affected. Renal clearance of the hydroxy metabolites does decrease with age (Nelson *et al.* 1988a; Young *et al.* 1984). As a result, concentrations of hydroxynortriptyline may be substantially elevated in older patients.

In children, the clearance of tricyclic compounds is increased. Half-lives of imipramine are shorter and ratios of desmethylimipramine to imipramine are higher, consistent with more rapid metabolism (Geller 1991; Rapoport and Potter 1981). However, a study of desipramine in children reported that the clearance of both desipramine and hydroxydesipramine was increased, so ratios of the hydroxy metabolite to the parent compound were not elevated (Wilens *et al.* 1992).

Relationship of Plasma Concentration to Clinical Action

Plasma Concentration and Response

Marked interindividual variability of tricyclic plasma concentrations was described by Hammer and Sjoqvist (1967). This finding suggested that drug-level monitoring might ensure that therapeutic blood levels are achieved and might help avoid toxic levels. In carefully selected inpatients with endogenous or melancholic major depressive disorder, treatment with adequate levels of imipramine or desipramine resulted in robust response rates of approximately 85% (Glassman *et al.* 1977; Nelson *et al.* 1982). However, similar relationships have proven difficult to demonstrate in outpatients with depression. In outpatients, drug-placebo differences are often small, and the effect of drug treatment is harder to detect. Outpatients with depression may be more heterogeneous and may include individuals who are not responsive to any drug treatment. It is logical to conclude that blood-level relationships determined for inpatients with severe depression might be used as a guide to treat outpatients, but this assumption has not been empirically validated.

The American Psychiatric Association Task Force on the Use of Laboratory Tests in Psychiatry (1985) reviewed studies relating tricyclic plasma levels and response. Its members concluded that a relationship had been demonstrated for imipramine, desipramine, and nortriptyline (see Table 11-2). Data on the relationship between blood level and response in depression are limited or conflicting for the other tricyclic and tetracyclic compounds.

Plasma Concentration and Toxicity

Blood-level monitoring may help avoid toxicity. Delirium, cardiac conduction delay, and seizure are associated with elevated tricyclic plasma concentrations (Livingston *et al.* 1983; Preskorn and Irwin 1982; Preskorn and Simpson 1982). Following overdose, tricyclic blood levels greater than 1,000 ng/mL can be achieved, and the risks of delirium, stupor, cardiac abnormalities, and seizures are all substantially increased (Nelson and Spyker 2017; Preskorn and Irwin 1982; Rudorfer and Young 1980; Spiker *et al.* 1975). The value of blood-level monitoring to avoid serious adverse effects has been difficult to demonstrate because rates of serious toxicity are low; large samples are required to demonstrate any increase in risk at higher blood levels.

If blood-level monitoring is undertaken, the clinician should bear in mind that many factors--including laboratory variability, blood sampling errors, missed doses, and biological variability--can affect drug concentrations. For this reason, the clinician should not view the concentration reported as a precise measure. Because concentrations vary across such a wide range, it may be very helpful to know whether the level is low, moderate, or high.

Dosage-Adjustment Techniques

The demonstrated relationship between timed drug concentrations after a single tricyclic dose and the steady-state level achieved indicates that plasma levels could be used to rapidly adjust dose; however, laboratory constraints make this impractical. A more clinically feasible method is to start the drug at a low or moderate fixed dosage, obtain a patient blood sample after 5-7 days of administration, and then make further adjustments based on that level. There are exceptions. Elderly patients with depression often require gradual dosing to assess tolerance. For patients with panic attacks, lower starting dosages are used to avoid exacerbation. Doxepin and nortriptyline are available as oral solutions for patients who may not be able to tolerate tablets or capsules or for adjusting very low dosages.

Mechanism of Action

In early studies, investigators observed that the tricyclic agents blocked uptake of monoamines at the norepinephrine and serotonin transporters (Axelrod *et al.* 1961). This drug effect was quickly put forward as a possible mechanism of action. The observation that reserpine, which depletes presynaptic catecholamines, might induce depression in vulnerable individuals was consistent with this hypothesis (Goodwin and Bunney 1971). Confirmation that norepinephrine and serotonin do, in fact, mediate the action of monoamine reuptake inhibitors was provided by subsequent challenge studies in patients with depression. For example, administration of a tryptophan-free diet rapidly depleted serotonin and caused relapse among patients with depression who were successfully treated with a serotonin reuptake inhibitor but not a norepinephrine reuptake inhibitor (Delgado *et al.* 1990). In addition, administration of a-methyl-*p*-tyrosine, which interrupts the synthesis of catecholamines, caused relapse among patients who were successfully treated with noradrenergic agents but not among those receiving serotonergic drugs (Delgado *et al.* 1993). These studies provide supporting evidence that serotonin and norepinephrine mediate antidepressant effects, but they do not necessarily imply that alterations in these neurotransmitter systems are central to the etiology of depression.

Subsequent research on the mechanism of action of the tricyclics and other antidepressant drugs has shifted to also consider factors affecting postsynaptic signal transduction (Manji *et al.* 1995). Such factors include the coupling of G proteins to the adrenergic receptor or to adenylyl cyclase and the activity of membrane phospholipases and protein kinases. Other newer targets, including glucocorticoid receptors (Barden 1996), neurotrophic factors (Duman *et al.* 1997), and gene expression (Lesch and Manji 1992; Nibuya *et al.* 1996; Schwaninger *et al.* 1995), have been explored.

Indications and Efficacy

Major Depressive Disorder

The efficacy of tricyclic and tetracyclic compounds in major depressive disorder is well established (Agency for Health Care Policy and Research 1993; Davis and Glassman 1989). Imipramine is the most extensively studied tricyclic antidepressant, in part because new drugs are often compared with it. In 30 of 44 placebo-controlled studies, imipramine was more effective than placebo. If data from these studies are combined, 65% of 1,334 patients *completing* treatment with imipramine were substantially improved, whereas 30% of those taking placebo improved. *Intention-to-treat* response rates for placebo-controlled studies of imipramine in outpatients were 51% for imipramine and 30% for placebo (Agency for Health Care Policy and Research 1993). The other tricyclic and tetracyclic antidepressants appeared comparable to imipramine in efficacy.

The tricyclic compounds are also effective when used for maintenance treatment. Frank *et al.* (1990) found that imipramine, at the full dosage, effectively maintained improvement for nearly 80% of patients with depression for a 3-year period, whereas only 10% of the placebo group achieved this outcome. In this study, maintenance psychotherapy had an intermediate effect, with approximately 30% of patients remaining well. In practice, clinicians may encounter patients with chronic depression, residual symptoms, or comorbid medical and psychiatric disorders. For such patients, the effects of acute and maintenance treatment are less robust.

The FDA has approved all of the tricyclic and tetracyclic compounds discussed in this chapter for the treatment of depression, with the exception of clomipramine, which is approved for OCD only. In Europe, clomipramine is also used for depression; in fact, it has been regarded by many as the most potent antidepressant.

Major Depressive Disorder With Melancholic Features (Severe Depression)

The efficacy of tricyclic compounds seems to vary in different subtypes of depression. Early studies of tricyclic compounds were frequently conducted with hospitalized patients with depressive disorder with melancholic features (severe depression). Tricyclic antidepressants were effective for these patients. In fact, the tricyclics may be especially effective in this group. Two studies of imipramine and desipramine reported response rates of approximately 85% for hospitalized patients with severe depression who did not have a history of treatment-resistant depression, did not have prominent personality disorder, received an adequate dosage and attained an adequate plasma concentration of the drug, and completed treatment (Glassman *et al.* 1977; Nelson *et al.* 1982).

When the SSRIs were introduced, it was suggested that they might be less effective than the tricyclic antidepressants in treating severe or melancholic depression. However, in a large meta-analysis of more than 100 comparison studies, Anderson (2000) found that tricyclic antidepressants and SSRIs had comparable efficacy. In a separate meta-analysis of 25 inpatient studies (Anderson 1998), the advantage of the tricyclics appeared limited to those with dual action--namely, amitriptyline and clomipramine. In outpatient populations, the designation of melancholia does not appear to predict an advantage for tricyclic antidepressants versus SSRIs (Anderson and Tomenson 1994; Montgomery 1989).

Major Depressive Disorder With Anxious Distress

The use of tricyclics to treat anxious depression--or *depressive disorder with anxious distress* in DSM-5 (American Psychiatric Association 2013)--has been studied frequently. Doxepin, amoxapine, and maprotiline are FDA approved for use in patients with depression and symptoms of anxiety. Direct comparison studies, however, have shown little indication that one tricyclic is better than another for treatment of depression

with anxious distress. Compared with depressed patients who are not prominently anxious, depressed patients who are anxious may respond less well to amitriptyline (Kupfer and Spiker 1981), imipramine (Roose *et al.* 1986), and desipramine (Nelson *et al.* 1994). Yet these drugs are still more effective than placebo for individuals with depression and anxiety, and it is not established that another drug class is more effective for these patients.

Depressive Disorder With Atypical Features

A series of studies examined the efficacy of imipramine for patients with depressive disorder with atypical features (Liebowitz *et al.* 1984, 1988). Imipramine was more effective than placebo but significantly less effective than the monoamine oxidase inhibitor (MAOI) phenelzine. Other investigators have reported the value of switching from a tricyclic to an MAOI for patients with tricyclic-refractory depression with atypical features (McGrath *et al.* 1987; Thase *et al.* 1992). In fact, the utility of the diagnosis of atypical depression was supported in large part by the differential response to these drug classes.

Major Depressive Disorder With Psychotic Features

Glassman *et al.* (1975) observed that imipramine was less effective for patients with major depressive disorder who had delusions. Subsequently, Chan *et al.* (1987) reviewed several studies involving more than 1,000 patients and found that antidepressants--usually tricyclics--given alone were effective for approximately two-thirds of patients with depression without psychotic features but only for about one-third of individuals with depressive disorder with psychotic features. Several open-label studies reviewed elsewhere (Nelson 1987) and one prospective study (Spiker *et al.* 1985) reported that the tricyclics, when combined with an antipsychotic, are effective in treating psychotic depression.

Anton and Burch (1990) suggested that because of its antipsychotic effects, amoxapine might be effective for depressive disorder with psychotic features. In a double-blind study, they demonstrated that amoxapine was comparable in efficacy to the combination of perphenazine and amitriptyline in treating psychotic depression (Anton and Burch 1990).

Major Depressive Episodes in Bipolar Disorder

Fifty years ago, MAOI antidepressants were suggested to be more effective than the tricyclics in treating depressive episodes in bipolar disorder (Himmelhoch *et al.* 1972). Later, Himmelhoch *et al.* (1991) demonstrated in a double-blind study that tranylcypromine was more effective than imipramine for bipolar depression. Because tricyclics are more likely than other agents to induce mania (Wehr and Goodwin 1987), they are not recommended for monotherapy of bipolar disorders.

Persistent Depressive Disorder

The new DSM-5 diagnostic category *persistent depressive disorder* includes both chronic major depressive disorder and the previous DSM-IV (American Psychiatric Association 1994) diagnosis dysthymic disorder. Imipramine appears to be effective in treating chronic depression and to be relatively comparable to sertraline in efficacy (Keller *et al.* 1998; Kocsis *et al.* 1988). Imipramine and desipramine have both been studied in controlled trials in chronic depression. Imipramine was more effective than placebo for the acute treatment of DSM-III-TR (American Psychiatric Association 1987)-defined dysthymia (Thase *et al.* 1996), and desipramine was more effective than placebo for maintenance treatment (Miller *et al.* 2001).

Major Depressive Disorder in Older Adults

Gerson *et al.* (1988) reviewed studies of tricyclic antidepressants in older patients reported prior to 1986. They found 13 placebo-controlled trials but noted several methodological problems. Although tricyclics were effective, the overall response rates for older patients appeared to be lower than those for nonelderly patients (Agency for Health Care Policy and Research 1993). Katz *et al.* (1990) conducted one of the first placebo-controlled trials examining nortriptyline in the treatment of patients older than 80 years living in a residential care facility. Nortriptyline was more effective than placebo. The dosages used and levels achieved were similar to those in younger individuals. This investigation by Katz *et al.* (1990) remains the only one to date showing an advantage for an antidepressant over placebo in nursing home patients with depression.

Depressive Disorders in Children

In children and adolescents with depression, the tricyclic antidepressants have not demonstrated superiority over placebo (Ryan 1992).

Panic Disorder

Although none of the tricyclic or tetracyclic drugs are approved for use in panic disorder, imipramine was the first drug described for such use (Klein 1964). The efficacy of both tertiary and secondary tricyclics has been demonstrated in controlled trials (Jobson *et al.* 1978; Munjack *et al.* 1988; Zitrin *et al.* 1980). In treating panic disorder, the drug is initiated at a low dose to avoid exacerbation of panic symptoms.

Obsessive-Compulsive Disorder

Unlike depression, which responds to a variety of antidepressant agents, OCD appears to require treatment with a serotonergic agent. Clomipramine, the most serotonergic of the tricyclics, is FDA approved for use in OCD, and its efficacy in this disorder is well established (Greist *et al.* 1995). Studies comparing the effectiveness of clomipramine with that of noradrenergic agents such as desipramine reported that clomipramine was substantially superior (Leonard *et al.* 1989). Although the SSRIs are effective in treating OCD, clomipramine has been suggested to be superior (Greist *et al.* 1995). Whether this suggested superiority is attributable to the dual mechanism of clomipramine or to other factors is unclear.

Attention-Deficit/Hyperactivity Disorder

The efficacy of the stimulant drugs in treating ADHD is well established. The tricyclics, especially desipramine, also appear to be of value. In one study, desipramine (at dosages greater than 4 mg/kg) given for 3-4 weeks was effective for two-thirds of children, whereas placebo was effective for only 10% (Biederman *et al.* 1989). Desipramine

was also found to be more effective than placebo for adults with ADHD (Wilens *et al.* 1996). One advantage of desipramine is its low potential for abuse. Unfortunately, five cases of sudden death in children (all younger than age 12 years) treated with desipramine were reported in the early 1990s (Riddle *et al.* 1991, 1993). As a result, desipramine is contraindicated for children younger than age 12 years (discussed in greater detail in "Side Effects and Toxicology"). Given that tricyclics as a group share similar adverse cardiac effects, there is reason to be concerned that other tricyclics might also have safety issues in young children (see also Chapter 60, "Treatment of Child and Adolescent Disorders").

Pain Syndromes

The tricyclics and the tetracyclic maprotiline have been widely used in various chronic pain syndromes. In a review of the literature, O'Malley *et al.* (1999) identified 56 controlled studies involving tricyclic antidepressant therapy for various pain syndromes, including headache (21 studies), fibromyalgia (18 studies), functional gastrointestinal syndromes (11 studies), idiopathic pain (8 studies), and tinnitus (2 studies). Salerno *et al.* (2002) identified seven more placebo-controlled trials of tricyclics or maprotiline used for chronic back pain. These agents were quite effective; the mean effect size (0.87) and the number needed to treat (approximately three) in the pain trials were more robust than those usually observed in placebo-controlled studies of depression. Therefore, the analgesic activity of these compounds was not simply the result of their antidepressant effects.

The mechanism of these agents' analgesic effects appears to differ from that of their antidepressant effects. The antinociceptive actions of antidepressants result from actions on descending norepinephrine and serotonin pathways in the spinal cord (Yoshimura and Furue 2006). In animals, the antinociceptive effects of norepinephrine reuptake inhibitors and combined norepinephrine-serotonin reuptake inhibitors seem to be more potent than those of SSRIs (Mochizucki 2004). In humans, there is some evidence that the combined-action agents amitriptyline and clomipramine are more effective than selective agents (Eberhard *et al.* 1988; Max *et al.* 1992; Panerai *et al.* 1990). In humans, antidepressant dosing and timing of effects for pain differ from those for depression. For example, the usual dosages of amitriptyline required for pain management (approximately 75 mg/day) are lower than those required to treat depression (150-300 mg/day) and response occurs more quickly, usually within the first 1 or 2 weeks.

Other Indications

Imipramine is FDA approved for the treatment of nocturnal enuresis in children, and controlled trials indicate efficacy (Rapoport *et al.* 1980). The dose of imipramine is usually 25-50 mg taken at bedtime. Amitriptyline and nortriptyline also appear to be useful for this indication, although they are not FDA approved for use in this disorder. Their mechanism of action is unclear but may in part be anticholinergic. Given the serious cardiac risks associated with desipramine use for children younger than 12 years (see the earlier subsection "Attention-Deficit/Hyperactivity Disorder"), use of tricyclics other than desipramine might also pose safety risks for this population. However, the low imipramine doses used to treat pediatric nocturnal enuresis may reduce this risk.

Tricyclic antidepressants have been extensively studied in patients with schizophrenia. However, in the absence of a major depressive episode, these agents appear to be of limited value (Siris *et al.* 1978).

The more sedating tricyclics have been used to treat insomnia. Oral doxepin (Silenor) at low dosages acts primarily as a histaminic antagonist and is FDA approved for insomnia. Because of its antihistaminic effects, topical doxepin (Zonalon 5% topical cream) has also been used for pruritus and is FDA indicated for short-term management of moderate pruritus in atopic dermatitis and lichen simplex chronicus.

Side Effects and Toxicology

Distinguishing side effects during tricyclic treatment from the somatic symptoms of depression can be complicated. During treatment, patients may attribute somatic symptoms to drug side effects even if the symptoms were preexisting (Nelson *et al.* 1984).

Another general factor contributing to side effects is patient vulnerability. For example, the presence of orthostatic hypotension prior to treatment is associated with orthostatic hypotension during treatment (Glassman *et al.* 1979). Seizures are most likely for a patient with a history of them (Rosenstein *et al.* 1993). Cardiac conduction problems are most likely for patients with a preexisting conduction delay (Roose *et al.* 1987a).

Antidepressant drugs affect a variety of organs and can produce adverse effects. The in vitro potency or affinity of antidepressant compounds for various receptor sites (see Table 11-1) is one factor determining the likelihood that specific side effects will be produced. A related issue is how the potency of a secondary effect relates to that of the primary action of the drug. If the secondary effect is more potent, it will occur at concentrations below the therapeutic level of the drug. For example, orthostatic hypotension often occurs at low plasma concentrations, and the antihistaminic effects of doxepin occur at doses well below antidepressant doses. Conversely, the proarrhythmic and proconvulsant effects of the tricyclic antidepressants become more pronounced at elevated blood levels or those encountered in overdose.

Central Nervous System Effects

The principal action of the tricyclic and tetracyclic agents in the CNS is to reduce the symptoms of depression. Nondepressed subjects given imipramine may feel sleepy, quieter, light-headed, clumsy, and tired. These effects are generally unpleasant (Dimascio *et al.* 1964).

The anticholinergic and antihistaminic effects of tricyclic and tetracyclic antidepressants can produce confusion or delirium. The incidence of delirium is dose dependent, with the risk for delirium increasing at blood levels greater than 300 ng/mL (Livingston *et al.* 1983; Preskorn and Simpson 1982). Delirium risk appears to be higher with the more anticholinergic agents such as amitriptyline. Patients with concurrent dementia are particularly vulnerable to the development of delirium, and the more anticholinergic tricyclics should be avoided these individuals. Intramuscular or intravenous physostigmine can be used to reverse or reduce delirium symptoms, but physostigmine has a short duration of action that makes its continued use difficult.

Seizures can occur with all of the tricyclic and tetracyclic agents and are related to dosage and blood level (Rosenstein *et al.* 1993). For clomipramine, seizure risk is reported to be 0.5% at dosages up to 250 mg/day, but at dosages of 300 mg/day or greater, seizure risk increases to 2.1% (McTavish and Benfield 1990). The seizure risk for imipramine and amitriptyline was not well established at the time of marketing. Two postmarketing studies reported that seizure risks varied from 0 to 0.6% or 0.7% for various tricyclic compounds and were clearly dose related (Jick *et al.* 1983; Peck *et al.* 1983). Seizure risk is substantially increased following overdose (Spiker *et al.* 1975). Cumulative data to date suggest that amoxapine, clomipramine, and maprotiline present the highest seizure risk among these agents (Johannessen Landmark *et al.* 2016). Seizure risk is increased for patients with predisposing factors such as a history of seizures, the presence of a brain injury, or the use of antipsychotics. The mechanism by which tricyclics produce seizures is not well understood.

A fine, rapid tremor can occur with the use of tricyclic agents. Because tremors are dose dependent, they tend to occur at higher blood levels. Development of a tremor may indicate an elevated blood level (Nelson *et al.* 1984).

Because the 7-hydroxy metabolite of amoxapine has antipsychotic properties, administration of amoxapine carries the potential risk for neuroleptic malignant syndrome and tardive dyskinesia. Although these adverse events are rare, the seriousness of the risk and the availability of alternatives suggest that amoxapine should be reserved for indications that warrant medication with antipsychotic properties.

Anticholinergic Effects

The tricyclics block muscarinic receptors and can cause a variety of anticholinergic side effects such as dry mouth, constipation, blurred vision, and urinary hesitancy. The tricyclic and tetracyclic compounds vary substantially in their muscarinic potency (see Table 11-1). Amitriptyline is the most potent, and desipramine is the least anticholinergic. Amoxapine and maprotiline also have minimal anticholinergic effects.

Although anticholinergic effects are bothersome, they are usually not serious. These effects can, however, become severe. An ocular crisis in patients with narrow-angle glaucoma can occur, and this acute condition is associated with severe pain. Urinary retention can be associated with stretch injuries to the bladder. Constipation can progress to severe obstipation. (Paralytic ileus has been described but is rare.) In these conditions, the medication must be discontinued and appropriate supportive measures instituted. Elderly patients are at greatest risk for severe adverse events. The incidence of severe anticholinergic adverse reactions is increased by concomitant administration of other anticholinergic agents. Use of a tricyclic with weak anticholinergic properties, such as nortriptyline or desipramine, can help reduce the likelihood of these adverse effects.

Anticholinergic side effects may benefit from other interventions. Bethanechol (Urecholine; 25 mg tid or qid) may be helpful for patients with urinary hesitancy. The regular use of stool softeners helps manage constipation. Patients with narrow-angle glaucoma who are receiving pilocarpine eye drops regularly can be treated with a tricyclic, as can those who have had an iridectomy. Tricyclic agents do not affect patients with chronic open-angle glaucoma.

Antihistaminic Effects

Several of the tricyclic compounds and maprotiline have clinically significant antihistaminic effects. Doxepin, the most potent H_1 receptor antagonist among the tricyclics, is more potent than diphenhydramine but less potent than mirtazapine. Central H_1 receptor blockade can contribute to sedation and delirium and appears to be related to increased appetite and associated weight gain. Because of their sedating effects, the tricyclic antidepressants, especially amitriptyline, have been used as hypnotics. Given their cardiac effects and lethality in overdose, this practice should be discouraged.

Cardiovascular Effects

Orthostatic hypotension is one of the most common reasons for discontinuation of tricyclic antidepressant treatment (Glassman *et al.* 1979). This effect can occur with all of the tricyclics but appears to be less pronounced with nortriptyline (Roose *et al.* 1981; Thayssen *et al.* 1981). The a_1-adrenergic blockade associated with the tricyclics contributes to orthostatic hypotension; however, the postural reflex is primarily affected. Resting supine blood pressure may be unaffected or can even be elevated (Walsh *et al.* 1992). Orthostatic hypotension is most likely to occur or is most severe among patients with preexisting orthostatic hypotension (Glassman *et al.* 1979). This condition is also aggravated by concurrent antihypertensive medications, especially volume-depleting diuretic agents. Elderly individuals are more likely to have preexisting hypotension and are also more vulnerable to the consequences of orthostatic hypotension, such as falls and hip fractures.

Orthostatic hypotension often occurs at low medication blood levels. Gradual dosage adjustment may allow accommodation to the subjective experience of light-headedness, but the actual orthostatic blood pressure changes do not accommodate within a reasonable period (e.g., 4 weeks) (Roose *et al.* 1998). Consequently, tricyclic antidepressants may not be suitable for patients who experience serious symptomatic orthostatic hypotension. Fludrocortisone (Florinef) has been used to raise blood pressure, but in this author's experience is not very effective. If patients are receiving antihypertensives, it may be possible and helpful to reduce the dosage of these agents.

Desipramine has been reported to raise *supine* blood pressure in young women (ages 18-45 years), although it is not clear that this effect is limited to that age group (Walsh *et al.* 1992). The elevation in blood pressure may be similar to that reported for venlafaxine.

Tachycardia occurs with all of the tricyclics, not just the more anticholinergic agents. Both supine and postural pulse changes can occur, and the standing pulse can be markedly elevated. In a study of nortriptyline dosed to a therapeutic plasma concentration, investigators found a mean pulse increase of 11% (8 beats per minute) (Roose *et al.* 1998). Patients do not accommodate to the pulse rise, which can persist for months (Rosenstein and Nelson 1991). Tachycardia is more prominent in young patients, who appear to be more sensitive to sympathomimetic effects, and is one of the most common reasons for drug discontinuation among adolescents. A persistent pulse rise, however, increases cardiac work and may be clinically significant for patients with ischemic heart disease.

The effect of tricyclic antidepressants on cardiac conduction has been a subject of great interest. Cardiac arrhythmia is the principal cause of death after tricyclic overdose (Spiker *et al.* 1975). Apparently, through inhibition of sodium/potassium adenosine triphosphatase, the tricyclics stabilize electrically excitable membranes and delay conduction, particularly His ventricular conduction. Consequently, the tricyclics have type I antiarrhythmic qualities or quinidine-like effects.

At therapeutic blood levels, tricyclic antidepressants can have beneficial effects on ventricular excitability. However, tricyclics can cause heart block in patients with preexisting conduction delay (Glassman and Bigger 1981; Roose *et al.* 1987b). A pretreatment QTc interval of 450 milliseconds or greater indicates that conduction is already delayed and the patient is not a candidate for tricyclic treatment. High drug plasma levels (e.g., imipramine plasma concentrations > 350 ng/mL) increase the risk of first-degree atrioventricular heart block (Preskorn and Irwin 1982). The tricyclic antidepressants do not reduce cardiac contractility or cardiac output (Roose *et al.* 1987a).

Glassman *et al.* (1993), noting that the type I antiarrhythmic drugs routinely given after myocardial infarction actually increase the risk of sudden death, suggested that the tricyclics may pose similar risks. The risk of sudden death is also increased when heart rate variability is reduced, and the tricyclics reduce heart rate variability (Roose *et al.* 1998).

As mentioned earlier in the subsection "Attention-Deficit/Hyperactivity Disorder," five cases of sudden death were reported in children younger than age 12 years who were receiving desipramine (Riddle *et al.* 1991, 1993). It was suggested that the immature conduction system in some children might render them more vulnerable to the cardiac effects of desipramine. However, no cardiac abnormalities were observed in a study of 71 children with 24-hour cardiac monitoring (Biederman *et al.* 1993). These findings suggest that cardiac events in children are not dose dependent and that electrocardiogram monitoring is not likely to identify those at risk.

Hepatic Effects

Acute hepatitis has been associated with the use of imipramine (Horst *et al.* 1980; Moskovitz *et al.* 1982; Weaver *et al.* 1977) or desipramine (Powell *et al.* 1968; Price *et al.* 1983). Mild increases in liver enzymes (less than three times the normal level) are not uncommon and usually can be monitored safely over a period of days or weeks. Enzyme changes do not appear to be related to drug concentrations (Price *et al.* 1984). Acute hepatitis is relatively uncommon but can occur. The etiology is not well established, but the condition seems to represent a hypersensitivity reaction in some cases. Tricyclic-induced acute hepatitis is characterized by very high enzyme levels (e.g., aspartate aminotransferase levels greater than 800 U/L), which develop within days. The enzyme pattern can be either hepatocellular or cholestatic. Enzyme changes may precede clinical symptoms, especially in the hepatocellular form. If a random blood test indicates mildly elevated liver enzymes, then enzyme levels can be followed for a few days. Because liver enzyme levels increase rapidly in acute hepatitis, the condition will become evident quickly and will be easily distinguished from persistent mild elevations in enzyme levels.

Acute hepatitis is dangerous and potentially fatal. If a patient develops this condition, the antidepressant must be discontinued and should not be introduced again because the next reaction may be more severe.

Other Side Effects

Increased sweating can occur with the tricyclic compounds; occasionally, sweating can be marked. Carbohydrate craving also can occur and can lead to significant weight gain when coupled with antihistaminic effects. Weight gain appears to be greater with the tertiary compounds than with the secondary agents. Sexual dysfunction has been described with the tricyclics but appears to be less common than with the SSRIs. This side effect appears to be associated with the more serotonergic compounds, such as clomipramine. Tricyclic antidepressants can cause allergic skin rashes, which are sometimes associated with photosensitivity reactions. Various blood dyscrasias also have been reported; fortunately, these are very rare.

Overdose

Because antidepressants are used by patients with depression who are at risk for overdose, the lethality of antidepressant drugs in overdose is of great concern. A tricyclic medication overdose of 10 times the total daily dosage can be fatal (Gram 1990; Rudorfer and Robins 1982). Death most commonly results from cardiac arrhythmia. However, seizures, CNS depression, and respiratory depression also can occur. Although the use of tricyclics in the treatment of depression has declined, amitriptyline remains widely used for other indications, such as pain. The total number of amitriptyline-associated deaths reported to U.S. poison control centers from 2000 to 2014 was greater than the total number of deaths associated with all other tricyclic and tetracyclic agents combined or the total number of deaths associated with all second-generation antidepressants (Nelson and Spyker 2017). All of the tricyclic and tetracyclic compounds can be dangerous in overdose. However, two reports indicated that the ratio of deaths to the number of prescriptions written was relatively low for clomipramine compared with the other tricyclic antidepressants (Cassidy and Henry 1987; Farmer and Pinder 1989). Among medications with at least 1,000 single drug exposures in the U.S. poison control database, clomipramine had significantly lower morbidity and mortality risks than the other tricyclic antidepressants (Nelson and Spyker 2017).

Teratogenicity

The long history of tricyclic use without observation of birth defects provides support for the safety of these agents. Of course, patients must be informed of the possible risks and benefits of taking these medications and the risks of discontinuation before they agree to treatment. The risk for recurrence is particularly high during or following pregnancy for patients with a prior history of depression.

If tricyclics are continued during pregnancy, dosage adjustment may be required because of metabolic changes (Altshuler and Hendrick 1996). The infant may experience drug withdrawal after delivery, which is characterized by tachypnea, cyanosis, irritability, and poor sucking reflex. Drugs in this class should be discontinued 1 week before delivery if possible. The tricyclics are excreted in breast milk at concentrations similar to those in plasma but the actual quantity delivered is very small, so drug levels in the infant are usually undetectable (Rudorfer and Potter 1997; also see Chapter 63, "Psychopharmacology During Pregnancy and Lactation").

Drug-Drug Interactions

Both pharmacodynamic and pharmacokinetic drug interactions should be considered.

Pharmacodynamic Interactions

Serious pharmacodynamic interactions can occur between the tricyclics and MAOIs. The most dangerous scenario--administration of a large dose of a tricyclic to a patient who is already taking an MAOI--could result in a sudden increase in catecholamines and a potentially fatal hypertensive reaction. Tricyclics and MAOIs have been used together to treat patients with refractory depression (Goldberg and Thornton 1978; Schuckit *et al.* 1971). When used in combination, treatment is begun at lower dosages and either the two compounds are started together or the tricyclic is started first.

The most common pharmacodynamic interaction involving the tricyclics occurs when they are added to other sedating agents, resulting in increased sedation. By blocking the norepinephrine transporters, the tricyclics block the uptake and thus interfere with the actions of guanethidine and tyramine. Desipramine and the other tricyclics reduce the effect of clonidine.

Quinidine is an example of a drug with a potential for dynamic and kinetic interaction with tricyclics. Because the tricyclics have quinidine-like effects, the effects of tricyclics and quinidine on cardiac conduction are potentially additive. In addition, quinidine is a potent CYP2D6 isoenzyme inhibitor that can increase tricyclic levels, further adding to the problem.

Pharmacokinetic Interactions

Several drugs can block the metabolic pathways of the tricyclics, resulting in higher and potentially toxic blood levels of drug. Desipramine has been of particular interest because it is metabolized via the CYP2D6 isoenzyme and there are no major alternative pathways. Inhibition of CYP2D6 can result in very high desipramine plasma levels, and toxicity can occur (Preskorn *et al.* 1990). As described in the previous section ("Pharmacodynamic Interactions"), quinidine is a very potent CYP2D6 inhibitor. Fluoxetine and paroxetine, duloxetine, bupropion, and some antipsychotics also inhibit CYP2D6. Fluoxetine and paroxetine at usual dosages increase desipramine levels, on average, three-to fourfold in individuals who are extensive metabolizers (Preskorn *et al.* 1994). CYP2D6 inhibitors would be expected to block nortriptyline metabolism, but the magnitude of this interaction has not been well studied.

Because the tertiary tricyclics are metabolized by several pathways (CYP1A2, CYP3A4, and CYP2C19), a selective inhibitor of one pathway would be unlikely to have a significant effect on their plasma levels. Although numerous drug interactions have been described, many are of doubtful clinical significance (for comprehensive reviews, see Nemeroff *et al.* 1996 and Pollock 1997).

Enzyme induction can also occur, which may render the tricyclic acted upon ineffective. Unlike enzyme inhibition, which occurs quickly, enzyme induction requires the synthesis of new enzymes and the full effect may take 2-3 weeks to develop. Barbiturates and carbamazepine are potent inducers of CYP3A4, which can become an important alternative pathway for some tricyclics.

Nicotine induces the CYP1A2 pathway and may lower concentrations of the tertiary tricyclics, but the secondary tricyclics (e.g., desipramine, nortriptyline) are less affected.

Acute ingestion of alcohol can reduce first-pass metabolism, resulting in higher tricyclic levels. This interaction is important because tricyclic overdose is often associated with alcohol ingestion. Conversely, chronic use of alcohol appears to induce hepatic isoenzymes and may lower tricyclic levels (Shoaf and Linnoila 1991).

The tricyclics themselves appear to be weak enzyme inhibitors, and few clinically significant interactions have been described. The tertiary tricyclics compete with warfarin for some metabolic enzymes (e.g., CYP1A2) and may increase warfarin levels.

Conclusion

The tricyclic drugs were the mainstay of treatment for depression for three decades. Although the second-generation antidepressants appear to be better tolerated, no new agent has been shown to be more effective than the tricyclics, and, if anything, there has been concern that the new agents may be less effective. The tricyclics were "dirty" drugs; that is, they had multiple actions. Although their side effects have been emphasized, these multiple actions may contribute to their efficacy. Not only does amitriptyline block uptake of serotonin, but its metabolite blocks uptake of norepinephrine, and amitriptyline is also a 5-HT_2 antagonist. Furthermore, the anticholinergic effects of amitriptyline may contribute to its antidepressant activity. The principal drawback of this class of agents is the risk for serious cardiac adverse effects. Tricyclics can aggravate arrhythmia in patients with a preexisting conduction delay. These agents also may increase the risk of sudden death in children and in patients with ischemic heart disease. Moreover, a week's supply of medication taken in overdose can be fatal. Because of these adverse effects, it is unlikely that there will be a resurgence of interest in tricyclic antidepressants. Nevertheless, the efficacy of these agents across a range of disorders, including pain, illustrates the potential advantages of antidepressant drugs with multiple actions.

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CHAPTER 12

Fluoxetine and Fluvoxamine

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Fluoxetine

The introduction of fluoxetine as the first selective serotonin reuptake inhibitor (SSRI) approved in the United States was a cultural phenomenon and an important advance in psychopharmacology. Considerable evidence has demonstrated that fluoxetine has a broad spectrum of clinical usefulness. There is a consensus, however, that the commercial success of fluoxetine (and subsequently marketed SSRIs) derives from its advantageous safety profile.

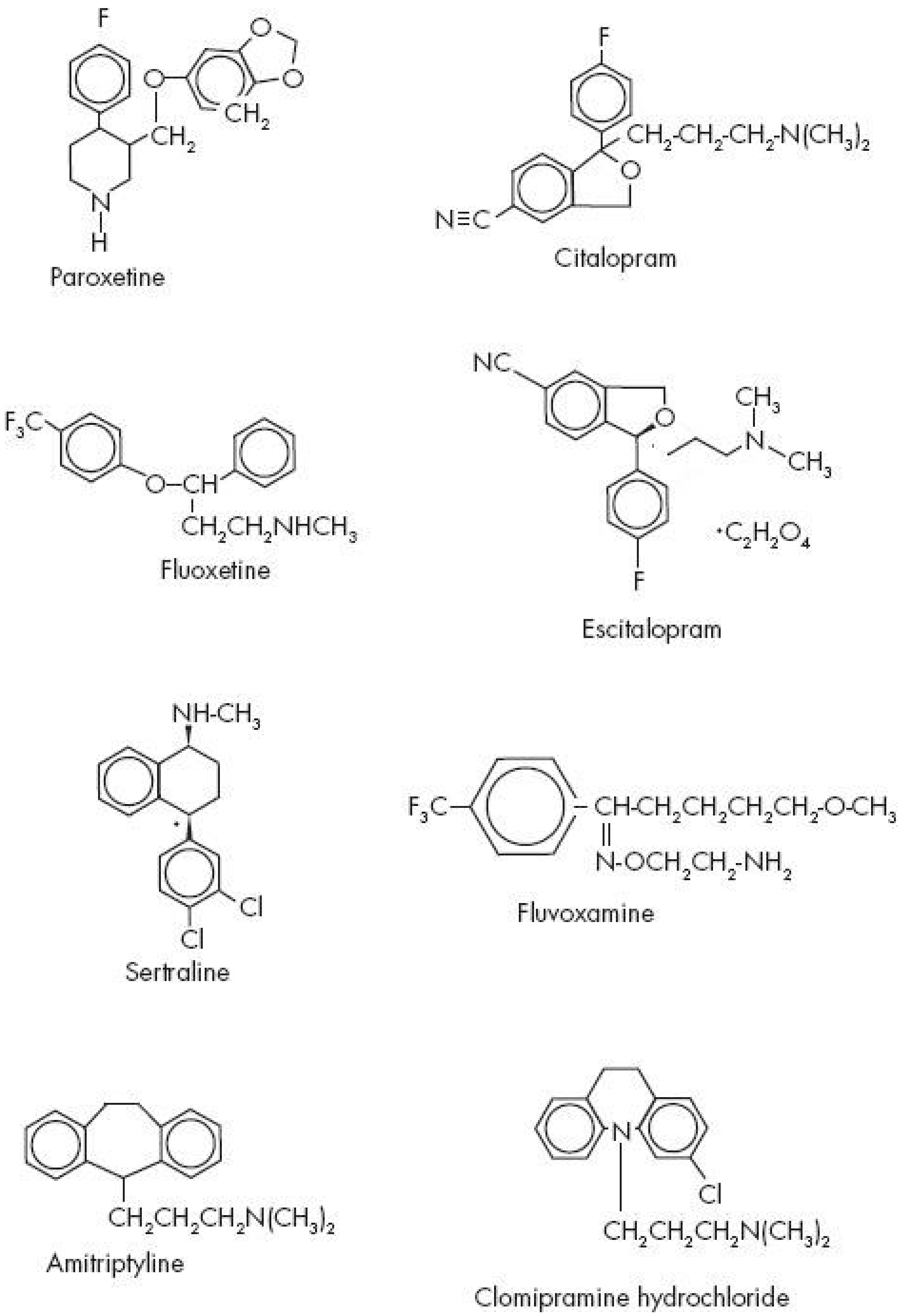
History and Discovery

Serotonin is an indoleamine with wide distribution in plants, animals, and humans. Pioneering histochemistry by Falck *et al.* (1962) demonstrated that serotonin was localized within specific neuronal pathways and cell bodies. These originate principally from two discrete nuclei: the medial and dorsal raphe. Although regional variations exist, several limbic structures manifest especially high levels of serotonin (Amin *et al.* 1954).

However, serotonin levels in the CNS represent only a small fraction of those in the body (Bradley 1989). Because serotonin does not cross the blood-brain barrier, it must be synthesized locally. Serotonin is released into the synapse from the cytoplasmic and vesicular reservoirs (Elks *et al.* 1979). Following its release, serotonin is principally inactivated by reuptake into nerve terminals through a sodium/potassium adenosine triphosphatase-dependent carrier (Shaskan and Snyder 1970). The transmitter is subsequently subjected to either degradation by monoamine oxidase (MAO) or vesicular storage. Abnormalities in central serotonin function have been hypothesized to underlie disturbances in mood, anxiety, satiety, cognition, aggression, and sexual drive, to highlight a few.

Structure-Activity Relations

Significant structural and activity differences exist among the SSRIs (Thomas *et al.* 1987). Their chemical structures help illustrate this diversity (Figure 12-1). In contrast to paroxetine and sertraline, which exist as single isomers, fluoxetine (like citalopram) is a racemate. Fluoxetine is less potent than paroxetine in vitro and less selective for serotonin reuptake inhibition than citalopram. However, in vitro potency does not necessarily equate with in vivo dosing experience, clinical efficacy, or adverse event profile.


F
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CH2
CH2
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H
Paroxetine
F
CH2-CH2-CH2-N(CH3)2
O
N≡C
Citalopram
F3C
O–CH
CH2CH2NHCH3
Fluoxetine
NC
O
CH3
N
CH3
•C2H2O4
F
Escitalopram
NH-CH3
Cl
Cl
Sertraline
F3C
CH-CH2CH2CH2CH2-O-CH3
N-OCH2CH2-NH2
Fluvoxamine
CH2CH2CH2N(CH3)2
Amitriptyline
N
Cl
CH2CH2CH2N(CH3)2
Clomipramine hydrochloride

FIGURE 12-1. Chemical structures of selective serotonin reuptake inhibitors and selected tricyclic antidepressants.

Although the tricyclic antidepressants (TCAs), like the SSRIs, antagonize serotonin receptors (Dempsey *et al.* 2005; Eisensamer *et al.* 2003), they also exhibit differing inhibitory activity at other receptor targets and consequently differ in their adverse event profiles (Hall and Ogren

1981; Snyder and Yamamura 1977; U'Prichard *et al.* 1978). These other targets include histaminergic, a$_1$-adrenergic, and muscarinic receptors. For fluoxetine, the median inhibitory concentration at histaminergic and adrenergic sites is in the micromolar range and thus unlikely to be of clinical significance. Activity at the muscarinic receptor is negligible for fluoxetine. Stauderman *et al.* (1992) reported that fluoxetine and paroxetine inhibited the binding of ^{3}H-labeled nitrendipine to L-type calcium channels; however, this was at concentrations that probably exceeded those reached during in vivo treatment of depression.

In summary, in vitro radioligand-binding techniques have shown that fluoxetine has a lower probability of many of the troublesome side effects associated with TCAs and is relatively selective in its serotonin reuptake inhibition.

Pharmacological Profile

Serotonin

The action of any SSRI extends beyond the inhibition of serotonin reuptake. At least 14 different serotonin receptor subtypes reside at pre-and postsynaptic locations (Fuller 1996). Serotonin$_{1A}$ (5-HT$_{1A}$) binding sites include both somatodendritic and presynaptic autoreceptors (which inhibit serotonin firing) and postsynaptic receptors. The latter are predominantly hippocampal, and their sensitivity is increased after chronic antidepressant exposure (Aghajanian *et al.* 1988; Castro *et al.* 2003).

After long-term administration, many antidepressants downregulate or reduce the density of serotonin$_2$ (5-HT$_2$) binding sites in the rat frontal cortex (Peroutka and Snyder 1980). Some, but not all, SSRIs have been associated with this effect (Fraser *et al.* 1988). Fluoxetine normalizes 5-HT$_{1A}$ density in rats (Sodero *et al.* 2006). SSRIs, as a drug class, normalize both 5-HT$_{1A}$ and 5-HT$_2$ receptor density in patients with depression (Leonard 1992).

The mechanisms by which fluoxetine and other SSRIs interact with the human serotonin transporter (SERT) are not fully understood. Some evidence suggests that the effect of fluoxetine on SERT is partially based on the presence of SERT promoter polymorphism, so it can either increase or decrease SERT expression, depending on an individual's genotype (Little *et al.* 2006). Further studies have shown that SERT may also be inhibited at the posttranslational stage, likely through multiple binding sites on the SERT molecule itself (Henry *et al.* 2006; Iceta *et al.* 2007).

Fluoxetine transiently inhibits dorsal raphe firing, decreases terminal autoreceptor function, and ultimately increases net serotonin synaptic transmission within hippocampal CA3 pyramidal cells (Blier *et al.* 1988). Electrophysiological studies indicate that most antidepressants enhance net serotonin transmission after chronic administration (Blier *et al.* 1990), albeit at different loci: the TCAs via enhanced sensitivity of postsynaptic 5-HT$_{1A}$ receptors, and the SSRIs (and MAO inhibitors [MAOIs]) via reduced sensitivity of somatodendritic (5-HT$_{1A}$) and terminal (serotonin$_{1D}$) autoreceptors. SSRIs and TCAs also exert an inhibitory effect on serotonin$_3$ receptors in a noncompetitive fashion (Eisensamer *et al.* 2003). These observations of different mechanisms may help explain why certain depressive symptoms that do not respond to one class of antidepressant respond to another class, and they may also explain the enhanced response to combinations of antidepressant agents.

Norepinephrine

Chronic administration of most somatic treatments for depression downregulates or reduces the density of a-adrenergic binding sites in the brain (Bergstrom and Kellar 1979). These treatments include traditional norepinephrine-specific and mixed uptake inhibitors (Charney *et al.* 1981). Results with the SSRIs have been less consistent (Johnson 1991). Fluoxetine induces a-adrenergic receptor downregulation and increases extracellular norepinephrine concentrations in the rat prefrontal cortex after acute systemic administration (Bymaster *et al.* 2002). Fluoxetine also potentiates the noradrenergic effects of bupropion (Li *et al.* 2002).

Most studies with SSRIs have not shown a consistent change in b-adrenergic binding or b-adrenergic-stimulated cyclic adenosine monophosphate production. However, Baron *et al.* (1988) reported that fluoxetine, when coadministered with desipramine, augmented the reduction in cortical b-adrenergic receptors expected with desipramine alone. In contrast, investigations with fluvoxamine, paroxetine, and citalopram have not yielded consistent results. In general, the greater the serotonin selectivity of a compound, the less in vitro evidence for b-adrenergic downregulation has been seen. Thus, b-adrenergic downregulation may not be essential for clinical efficacy.

Current data do not support a significant SSRI effect on a-adrenergic receptor affinity or density, and studies of fluoxetine (Wong *et al.* 1985) have shown relative inactivity at this site. Fluoxetine reduces desipramine-induced release of growth hormone after 4 weeks of treatment (O'Flynn *et al.* 1991), suggesting possible indirect activity at the a_2-adrenergic receptor.

In summary, although relative differences in adrenoreceptor affinity exist across the SSRI class and fluoxetine may have more adrenergic activity than some of the other SSRIs, these differences appear to have negligible clinical significance.

Dopamine

Animal studies provide evidence that the serotonergic system may exert tonic inhibition on the central dopaminergic system. In rats, serotonin also decreases the generation of dopaminergic cells from mesencephalic precursors--an effect mediated by $serotonin_4$ and $serotonin_7$ receptors found on glial cells (Parga *et al.* 2007). Thus, fluoxetine might

diminish dopaminergic transmission, consistent with anecdotes of extrapyramidal side effects occurring during fluoxetine therapy (Bouchard *et al.* 1989). Serotonin agonists, however, also exert a facilitatory influence on dopamine release (Benloucif and Galloway 1991) that can be antagonized by the 5-HT_1 blocker pindolol, and evidence suggests that SSRIs may actually sensitize mesolimbic dopamine receptors (Arnt *et al.* 1984a, 1984b). Furthermore, repeated administration of fluoxetine, citalopram, or paroxetine to rats increased spontaneous dopaminergic neuronal activity (Sekine *et al.* 2007). Chronic fluoxetine treatment also increased brain-derived neurotrophic factor (BDNF) expression in rat dopaminergic regions (Molteni *et al.* 2006).

Summary of Neurotransmitter Effects

Fluoxetine enhances central serotonin transmission through increased output and/or increased postsynaptic receptor sensitivity (Blier *et al.* 1987). Fluoxetine's overall influences on the noradrenergic and dopaminergic systems are less straightforward and less likely to play a role in the drug's antidepressant effects. However, clinical response in depression remains highly individualized and is not guaranteed by such changes in any of the neurotransmitter systems (Charney *et al.* 1984).

Formulations

Fluoxetine is available in the United States in immediate-release tablet, capsule, and oral solution formulations. There is also a 90-mg capsule containing delayed-release pellets, which is taken once weekly. This formulation is not bioequivalent with the immediate-release products, and it has separate dosing and administration instructions. The less frequently used formulations (e.g., solution and delayed-release capsule) may be subject to drug shortages, given that there are fewer suppliers of these formulations (U.S. Food and Drug Administration 2023).

A capsule formulation that combines fluoxetine with olanzapine is also available in multiple strengths.

Pharmacokinetics and Disposition

Considerable pharmacokinetic variability exists within the SSRI class (Leonard 1992). Moreover, discussion of drug half-life must also include consideration of any active metabolites. Fluoxetine is extensively metabolized by the liver's cytochrome P450 (CYP) system to its active metabolite, norfluoxetine. Fluoxetine is a potent CYP2D6 inhibitor; norfluoxetine has a moderate inhibitory effect on CYP3A4 (Hemeryck and Belpaire 2002). The elimination half-life of norfluoxetine (4-16 days) is significantly longer than that of fluoxetine (4-6 days); in fact, norfluoxetine's half-life is the longest of any of the SSRIs or their active metabolites. Half-life is not significantly affected by hemodialysis or renal impairment (Aronoff *et al.* 1984).

Fluoxetine's relatively long half-life confers greater protection from the discontinuation syndrome associated with abrupt stopping of or noncompliance with treatment. However, more prolonged vigilance is required for drug-drug interactions after fluoxetine discontinuation; for example, a 5-week washout from fluoxetine is recommended before initiating an MAOI (Ciraulo and Shader 1990; Lane and Baldwin 1997). Variability in drug half-life is associated with a range in time to steady-state plasma concentration, which does not clearly predict or correlate with onset of antidepressant activity.

Mechanism of Action

In the absence of pharmacological manipulation, the reuptake of serotonin into the presynaptic nerve terminal typically leads to its inactivation. Fluoxetine, by blocking the reuptake process, acutely enhances serotonergic neurotransmission by permitting serotonin to act for an extended period at synaptic binding sites. The net result is an acute increase in synaptic serotonin. One difference separating SSRIs from direct-acting agonists is that SSRIs are dependent on neuronal release of serotonin for their action--that is, they are not direct stimulators of postsynaptic receptor function and depend on presynaptic neuronal integrity. These pharmacodynamic features might explain SSRI nonresponse. If the release of serotonin from presynaptic neuronal storage sites was substantially compromised and, in turn, if the net synaptic serotonin concentration was negligible, a clinically meaningful response to an SSRI would not be expected.

Serotonin receptors also include a family of presynaptic autoreceptors that suppress the further release of serotonin, thus limiting postsynaptic receptor stimulation. de Montigny *et al.* (1989) suggested that the enhanced efficacy of serotonergic synaptic transmission is not the result of increased postsynaptic sensitivity. Rather, longer-term SSRI treatment induced a desensitization of somatodendritic and terminal serotonin autoreceptors. This desensitization would permit serotonin neurons to reestablish a normal rate of firing, despite sustained reuptake blockade. These neurons could then release a greater amount of serotonin into the synaptic cleft. This modification reportedly occurs over a time course that is compatible with the antidepressant response.

A newer theory of the mechanism of action of fluoxetine and other antidepressants (including other SSRIs, TCAs, MAOIs, ketamine, and esketamine) posits that the key to their efficacy is their ability to bind to the transmembrane domain of tyrosine kinase receptor 2 (TRKB) and thereby enhance the presence of TRKB at the neuronal membrane surface (Casarotto *et al.* 2021). This theory is based on what is known about the neurochemical actions of antidepressants and the investigators' findings in cultured neurons and in rodent behavioral testing. Casarotto *et al.* (2021) noted that antidepressants promote TRKB signaling, which in turn facilitates BDNF-induced neuronal plasticity. The authors demonstrated that fluoxetine (and imipramine, venlafaxine, moclobemide, ketamine, and esketamine) increased the surface expression of TRKB in cortical neurons. Casarotto and colleagues next demonstrated that the binding of fluoxetine (and other drugs) to TRKB influenced rodent learning and behaviors that are dependent on neuronal plasticity. Increased neuronal plasticity is known to produce the rewiring of abnormally wired networks that is required for all antidepressants' therapeutic effects. The authors hypothesized that the delay in therapeutic responses to SSRIs and TCAs is due to their gradual attainment of effective levels in brain, whereas ketamine readily penetrates the brain and quickly achieves synaptic concentrations sufficient to promote TRKB stimulation of BDNF-induced neuronal plasticity and circuit rewiring.

Indications and Efficacy

The FDA-labeled indications for fluoxetine are major depressive disorder, OCD, panic disorder, bulimia nervosa, and premenstrual dysphoric disorder.

We review these disorders as well as others for which fluoxetine is commonly used. Of note for adult patients, fluoxetine in combination with olanzapine is approved for acute treatment both of depressive episodes associated with bipolar I disorder and of treatment-resistant depression (Eli Lilly 2011).

Major Depressive Disorder

Placebo-controlled, double-blind trials have established the superiority of fluoxetine over placebo in the treatment of depression (Kasper *et al.* 1992). Statistically significant reductions in Hamilton Rating Scale for Depression (Hamilton 1960) scores from baseline have been seen as early as the second week of treatment; however, the rate and the quality of response to any SSRI are highly individualized (range, 10-42 days). Overall, the efficacy of fluoxetine has been found to be comparable to or slightly better than that of the conventional TCAs (Cipriani *et al.* 2005; Wernicke *et al.* 1987) and comparable to that of venlafaxine (Nemeroff *et al.* 2007; Schatzberg and Roose 2006). Within the class of SSRIs, there is no clear and consistent evidence for superior effectiveness of one agent over others (Kroenke *et al.* 2001).

In general, the range for dosage titration with most SSRIs is relatively narrow, and higher dosages are more often associated with increased adverse events (Altamura *et al.* 1988; Amin *et al.* 1989). Schweizer *et al.* (1990) reported that in a study of 108 patients treated with fluoxetine 20 mg/day for 3 weeks and then randomly assigned to receive either 20 mg or 60 mg/day for another 5 weeks, both groups did equally well after 8 weeks.

Early implementation of high-dosage therapy may be appropriate in some circumstances. Conversion of nonresponders by prescribing at the higher end of the dosage range has been described with fluoxetine (Fava *et al.* 1992). Unfortunately, plasma-level studies have contributed little to the understanding of the dose-response relationship (Kelly *et al.* 1989), likely because plasma levels do not accurately reflect synaptic concentrations and/or pharmacodynamic effects.

Continued efficacy of fluoxetine during maintenance therapy has been established in several trials (Danion 1989; Dufour 1987; Ferrey *et al.* 1989; Montgomery *et al.* 1988; Reimherr *et al.* 1998). One trial reported recurrence for 54 of 94 individuals who received placebo (57%) versus 23 of 88 participants continued on fluoxetine maintenance (26%) ($P < 0.0001$) who had at least 4.5 months of recovery before randomization (Montgomery *et al.* 1988).

Although fluoxetine is perceived as "activating," several studies have demonstrated its efficacy in depression featuring anxiety and psychomotor agitation (Beasley *et al.* 1991; Jouvent *et al.* 1989; Montgomery 1989).

To improve compliance with long-term treatment, a once-weekly 90-mg oral formulation was developed (Schmidt *et al.* 2000), but it has not attracted widespread use.

Obsessive-Compulsive Disorder

Clomipramine, a potent inhibitor of both serotonin and norepinephrine reuptake, was observed more than 50 years ago to reduce obsessive-compulsive symptoms (Van Renynghe de Voxvrie 1968). The superior benefit of this potent serotonergic TCA over desipramine represents a cornerstone in the serotonin hypothesis of OCD (Benkelfat *et al.* 1989). Fluoxetine is effective for OCD independent of a patient's comorbid

mood status (Jenike *et al.* 1989). For response to occur, patients with OCD may require higher dosages of medication and longer treatment periods than do patients with depression. Most patients do not experience substantial relief sooner than 4-6 weeks into a trial, and it may take 10-12 weeks for this to occur. In the American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Obsessive-Compulsive Disorder*, Koran *et al.* (2007) note that fluoxetine dosages up to 120 mg/day may occasionally be required and recommend that treatment continue for 1-2 years before a gradual taper is attempted. Currently, the SSRIs are considered a first-line treatment for OCD (Koran and Simpson 2013; Koran *et al.* 2007).

Fluoxetine has shown efficacy in children and adolescents with OCD, according to a meta-analysis of four randomized controlled trials (RCTs) (Maneeton *et al.* 2020). In addition, fluoxetine may be beneficial in some OCD spectrum disorders (placed in a separate chapter in DSM-5 [American Psychiatric Association 2013]), according to small controlled trials in excoriation disorder (Bloch *et al.* 2001; Simeon *et al.* 1997) and body dysmorphic disorder (Phillips *et al.* 2002).

Panic Disorder

SSRIs are the drugs of choice in the treatment of panic disorder and the prevention of panic attacks. Positive results from double-blind, placebo-controlled trials in patients with panic disorder are available for fluoxetine 10 and 20 mg/day (Michelson *et al.* 2001) and, in a 12-month SSRI comparison study, at a mean dosage of 27.8 mg/day (Dannon *et al.* 2007). In the long-term study, patients who continued their assigned SSRI had an excellent outcome (Dannon *et al.* 2007). Typically, a low dosage is used initially to minimize early side effects for patients with anxiety who are particularly sensitive to the disorder's somatic symptoms, and it sets the stage for long-term compliance.

Eating Disorders

Manipulation of central serotonin results in altered feeding behaviors (e.g., an increased satiety response) (Carruba *et al.* 1986). Blundell (1986) reported that pharmacological enhancement of serotonin reduced meal size, rate of eating, and body weight. The predominant locus of this serotonin effect is likely within the hypothalamus and may be mediated through gene expression of neuropeptide Y and proopiomelanocortin (Myung *et al.* 2005).

Bulimia nervosa. Clinical trials led the FDA to approve fluoxetine for the treatment of bulimia nervosa. Trials in which participants were administered fluoxetine 60 mg/day for 8 and 16 weeks showed a positive treatment effect on binge-eating and purging behaviors (Goldstein *et al.* 1995). A large double-blind, placebo-controlled 8-week study reported that fluoxetine 60 mg/day was more effective than 20 mg/day; the 20-mg dosage was more effective than placebo for only some outcomes (Fluoxetine Bulimia Nervosa Collaborative Study Group 1992). In a smaller study of 91 female patients in a primary care setting, those assigned to fluoxetine kept more physician appointments, exhibited greater reductions in binge eating and vomiting, and had greater improvement in psychological symptoms than those who received placebo (Walsh *et al.* 2004). Continued treatment with fluoxetine is associated with improvement and decreased risk of relapse (Romano *et al.* 2002).

Binge-eating disorder. Binge-eating disorder was officially listed with the Feeding and Eating Disorders in DSM-5. This disorder is characterized by recurrent binge-eating episodes, resultant marked distress, and absence of the compensatory behaviors seen in bulimia nervosa such as vomiting. In one RCT, fluoxetine was superior to placebo on some measures at 6 weeks (Arnold *et al.* 2002b), but in this and in a 16-week RCT (Grilo *et al.* 2005), fluoxetine was not associated at endpoint with superior binge-eating abstinence rates compared with placebo. In this trial, fluvoxamine was clearly inferior to cognitive-behavioral therapy (CBT) and did not enhance the outcome when added to CBT. Fluoxetine 60 mg/day far underperformed compared with CBT alone and did not improve outcome when added to CBT in two additional randomized trials (Grilo *et al.* 2012; Ricca *et al.* 2001), either at 24 weeks or at 1-year follow-up.

Anorexia nervosa. Pharmacological trials with SSRIs in patients with anorexia nervosa are less consistent. Kaye *et al.* (1991) suggested that fluoxetine may help maintain body weight in patients with anorexia nervosa who have gained weight. These investigators also completed a similar study with fluoxetine under controlled conditions, suggesting some benefit for fluoxetine in improving outcome and preventing relapse (Kaye *et al.* 2001). They reported that 10 of 16 patients given fluoxetine (target dosage of 60 mg/day) for 1 year had a significant reduction from baseline in measures of depression, anxiety, and OCD symptoms, whereas the 6 who discontinued did not. In a smaller 6-month follow-up study, the investigators found no benefit for these symptoms in 19 patients receiving an SSRI, of whom 7 received fluoxetine (Holtkamp *et al.* 2005). Walsh *et al.* (2006) found no benefit for continued treatment with fluoxetine after weight restoration in a double-blind RCT of 93 patients. The findings of all these studies are compromised by study participation refusal among eligible participants, small sample sizes, and high dropout rates.

Obesity. SSRIs have been extensively investigated for an effect on food consumption. This interest stems from evidence that perturbation of serotonin receptors modifies animal feeding behavior (Garattini *et al.* 1986). Serotonin innervation to the hypothalamus influences satiety and may selectively affect carbohydrate consumption (Wurtman *et al.* 1981). In one obesity treatment trial, 458 participants were administered fluoxetine (60 mg/day) or placebo for 52 weeks (Goldstein *et al.* 1994). Weight loss was significantly greater in the fluoxetine-treated group at 28 weeks but not at 52 weeks. In a randomized blinded study of children and adolescents, the effect on BMI was not greater at 12 or 24 weeks in the group randomly assigned to metformin plus fluoxetine (20 mg/day) than in those receiving metformin alone (Rezvanian *et al.* 2010). Long-term benefits may be better sustained when fluoxetine is combined with behavior modification (Marcus *et al.* 1990).

Premenstrual Dysphoric Disorder

Several blinded RCTs have established the efficacy and tolerability of fluoxetine in the treatment of premenstrual dysphoric disorder (Menkes *et al.* 1993; Pearlstein *et al.* 1997; Steiner *et al.* 1995; Su *et al.* 1993, 1997; Wood *et al.* 1992). In the largest study, 313 women with DSM-III-R late-luteal-phase dysphoric disorder (American Psychiatric Association 1987) received fluoxetine 20 mg/day, fluoxetine 60 mg/day, or placebo for six menstrual cycles after a two-cycle placebo washout period (Steiner *et al.* 1995). A total of 180 women completed the study. Both dosages of fluoxetine were superior

to placebo beginning at the first menstrual cycle and continuing throughout the six cycles. More patients treated with the 60-mg/day fluoxetine dosage discontinued because of adverse events compared with those administered

20 mg/day or placebo. More patients treated with placebo discontinued because of lack of response than did patients treated with either fluoxetine dosage. In a subsequent study of 34 women, fluoxetine was significantly superior to bupropion and placebo in treating premenstrual dysphoric disorder (Pearlstein *et al.* 1997). In a double-blind RCT of fluoxetine (10 or 20 mg/day) during the 14-day luteal phase, the 20-mg/day dosage but not the 10-mg/day dosage showed a significant advantage over placebo for the mood, physical, and social functioning symptoms of premenstrual dysphoric disorder; the 10-mg/day dosage was effective only for the mood symptoms (Cohen *et al.* 2002). A second luteal-phase study reported that fluoxetine 90 mg (e.g., a 90-mg controlled-release capsule taken once weekly) given 2 weeks and 1 week before expected menses was superior both to placebo and to 90 mg given 1 week before in improving measures of mood and social functioning but not physical symptoms (Miner *et al.* 2002).

Anger and Aggression

Diminished serotonergic activity has been implicated in impulsivity, anger, hostility, and aggression (Coccaro *et al.* 1989)--traits that are often encountered in Cluster B personality disorders (American Psychiatric Association 1994). Fluoxetine reduced impulsivity in small groups of patients with borderline personality disorder (Cornelius *et al.* 1991; Norden 1989). In two unpublished studies, however, fluoxetine (40 and 80 mg/day) was significantly less effective than dialectical behavior therapy in preventing suicide attempts within 6 or 12 months (Stoffers-Winterling *et al.* 2020). Fluoxetine significantly reduced the frequency of anger attacks in patients with and without depression; a dosage of 20 mg/day reduced the number of attacks to zero for more than two-thirds of patients with depression by 8 weeks (Fava *et al.* 1991, 1993, 1996; Rubey *et al.* 1996; Salzman *et al.* 1995).

Posttraumatic Stress Disorder

Fluoxetine significantly reduced symptoms of PTSD compared with placebo in 64 patients (veterans and nonveterans), as measured by the

Clinician-Administered PTSD Scale (van der Kolk *et al.* 1994). This medication also showed efficacy by week 6 in a large double-blind, placebo-controlled trial (Martenyi *et al.* 2002). However, the therapeutic effects of fluoxetine (and other SSRIs) are small compared with those of trauma-focused psychotherapies (Lee *et al.* 2016).

Premature (Early) Ejaculation

SSRIs, including fluoxetine, are effective in the treatment of premature ejaculation (Siroosbakht *et al.* 2019). Patients who do not respond to one SSRI (e.g., fluoxetine) often respond to another (Dadfar and Baghinia 2010; Murat Basar *et al.* 1999). In a 1-year follow-up study, patients treated with fluoxetine (20 mg/day or less) in combination with sexual behavior therapy reported significant improvement in ejaculation latency (Graziottin *et al.* 1996). Another study demonstrated efficacy from fluoxetine 90 mg administered weekly (Manasia *et al.* 2003).

Pain Syndromes

Fluoxetine has shown efficacy in reducing pain associated with diabetic neuropathy (Max *et al.* 1992) and fibromyalgia (Arnold *et al.* 2002a; Goldenberg *et al.* 1996). In addition, in two modest-sized, double-blind, placebo-controlled migraine headache trials (d'Amato *et al.* 1999; Saper *et al.* 1994), fluoxetine had a modest effect on overall headache status and total pain index scores after 2-3 months. Subsequent work demonstrated that antidepressants that also affect the norepinephrine system (i.e., serotonin-norepinephrine reuptake inhibitors) are more effective than the SSRIs in treating neuropathic pain (Mochizucki 2004; Pedersen *et al.* 2005).

Alcohol Use Disorder

A substantial amount of evidence from animal studies supports a serotonin dysfunction in alcohol abuse and dependence (Farren 1995). Although results are inconsistent, some clinical trials with SSRIs have reported reduced alcohol consumption in patients with and without depression in contrast with patients treated with TCAs, which have less robust efficacy (Cornelius *et al.* 1997; Lejoyeux 1996). However, a small 4-week double-blind study of fluoxetine (40 and 60 mg/day) reported no greater effect on alcohol intake than placebo (Naranjo *et al.* 1990). A 12-week, double-blind, placebo-controlled trial of fluoxetine in adolescents with alcohol use disorder and comorbid major depressive disorder found no difference from placebo in alcohol-or depression-related outcome variables (Cornelius *et al.* 2009). From a risk-benefit perspective, it is reassuring that fluoxetine does not appear to carry a high risk of fatal poisoning when taken in combination with alcohol (Koski *et al.* 2005).

Other Medical Conditions

Preliminary data support the efficacy of fluoxetine for patients who develop depression poststroke or after a cancer diagnosis. A 12-week double-blind RCT reported that early fluoxetine treatment of poststroke depression was more effective than placebo; open-label continuation treatment was more effective at 18 months of follow-up (Fruehwald *et al.* 2003). In a very large double-blind British RCT of patients with a clinical stroke diagnosis, investigators found that those assigned to fluoxetine were less likely to develop new depression at 6 months but had more bone fractures. Functional outcomes did not differ between the fluoxetine-and placebo-treated patients at 6 or 12 months (FOCUS Trial Collaboration 2019). A parallel study conducted in Sweden reported a similar result at 6 months (Lundstrom *et al.* 2020).

In one study, fluoxetine was not effective in treating postmenopausal hot flashes (Suvanto-Luukkonen *et al.* 2005). In a critical analysis, however, Loprinzi *et al.* (2009) pointed out that Suvanto-Luukkonen *et al.* (2005) did not use a no-treatment baseline measure, whereas two studies that did showed a positive effect of treatment.

At 6-month evaluation, fluoxetine was more effective than placebo in improving quality of life and reducing depressive symptoms in patients with early-stage breast cancer screened for depression (Navari *et al.* 2008). Fluoxetine's strong inhibition of CYP2D6 could, however, interfere with tamoxifen chemotherapy.

Two RCTs (Herscu *et al.* 2020; Reddihough *et al.* 2019) reported that fluoxetine and placebo had a similar effect on repetitive behaviors in children with autism spectrum disorder. A placebo-controlled pilot study of Crohn's disease also found no benefit from fluoxetine (Mikocka-Walus *et al.* 2017). Interestingly, fluoxetine may possess antiviral properties (Zuo *et al.* 2012). Two double-blind RCTs (Vercoulen *et al.* 1996; Wearden *et al.* 1998) of chronic fatigue syndrome found no greater effect from fluoxetine than placebo.

Side Effects and Toxicology

For most patients, SSRIs, including fluoxetine, are better tolerated than TCAs based on the number of early trial discontinuations attributable to an adverse event (see Boyer and Feighner 1991). For three-arm trials, the incidence of early discontinuation due to an adverse event was generally 5%-10% for placebo, 10%-20% for SSRIs, and 30%-35% for TCAs. The SSRIs, presumably by enhancing serotonin within the CNS, may induce agitation, anxiety, sleep disturbance, tremor, sexual dysfunction (primarily anorgasmia), or headache.

Because the enteric nervous system is richly innervated by serotonin, adverse events may include altered gastrointestinal motility and nausea. Certain autonomic adverse events, including dry mouth, sweating, and weight change, also occur. Furthermore, the use of SSRIs (including fluoxetine) during the perioperative period has been associated with a higher risk of adverse events, particularly bleeding events; however, the extent to which patient factors (e.g., medical illness) as opposed to the SSRIs themselves are responsible for the elevated risks remains unknown (Auerbach *et al.* 2013). Fluoxetine decreases rapid eye movement and increases non-rapid eye movement sleep at dosage ranges of 5-40 mg/kg in rodent models (Gao *et al.* 1992). This is a common property of many antidepressant medications.

As discussed earlier in this chapter, fluoxetine is unlikely to alter dopamine function. Nonetheless, some side effects, such as hyperprolactinemia, extrapyramidal symptoms, sexual and cognitive dysfunction, galactorrhea, mammary hypertrophy, and gynecomastia, have been attributed to the effects of SSRIs on the dopaminergic system (Damsa *et al.* 2004). Anecdotal reports of extrapyramidal side effects (Meltzer *et al.* 1979) associated with SSRIs are not more frequent than those reported historically with TCAs (Fann *et al.* 1976; Zubenko *et al.* 1987), MAOIs (Teusink *et al.* 1984), or trazodone (Papini *et al.* 1982). Very rare events, including arthralgia, lymphadenopathy, syndrome of inappropriate antidiuretic hormone secretion, agranulocytosis, and hypoglycemia, have been reported during clinical trials or postmarketing surveillance; however, causality typically is uncertain.

SSRIs, including fluoxetine, may increase the risk of bleeding if used concomitantly with antiplatelet drugs or anticoagulants. Some observational studies have found an association between SSRI use and bleeding complications (Auschra *et al.* 2022; Quinn *et al.* 2014).

One additional rare and life-threatening event associated with all SSRIs (and, more prominently, their interaction with MAOIs or other serotonin enhancers) is the central serotonin syndrome or *serotonin syndrome*. This phenomenon appears to represent an overactivation of central serotonin receptors and may manifest with features such as abdominal pain, diarrhea, sweating, fever, tachycardia, elevated blood pressure, altered mental state (e.g., delirium), myoclonus, increased motor activity, irritability, hostility, and mood change. Severe manifestations of this syndrome can induce hyperpyrexia, cardiovascular shock, or death. When a switch is being made from an SSRI to an MAOI, drug half-life (and that of any active metabolite, where applicable)

should serve as a guide to the length of the washout period. A standard recommendation is to wait at least five times the half-life of the SSRI or its metabolite, whichever is longer, before administering the next serotonergic agent (for a review, see Lane and Baldwin 1997). For fluoxetine, this means a minimum 5-week washout period.

Tolerance to an adverse event may change with dosage and/or length of exposure; higher dosages are typically associated with higher rates of adverse events (Bressa *et al.* 1989). Many events, such as activation (e.g., agitation, nervousness, insomnia), are typically transient (Beasley *et al.* 1991). Comparisons between morning and nighttime administration did not identify differences in efficacy (Usher *et al.* 1991).

In clinical trials, the incidence of increased heart rate or cardiac conduction disturbance has been very low with fluoxetine (Fisch 1985).

Suicidality

Evidence implicating serotonin depletion in suicide or violence is compelling. Reduced cerebrospinal fluid 5-hydroxyindoleacetic acid concentrations correlate highly with completed suicides in patients with depression (Edman *et al.* 1986; Ninan *et al.* 1984). In vitro binding assays have shown an increased density of 5-HT_2 receptors in individuals with depression and suicidal tendencies (Pandey *et al.* 1990). Both observations are consistent with a relative state of serotonin depletion among individuals with suicidal tendencies. The American College of Neuropsychopharmacology (1993) reviewed evidence showing that antidepressants result in substantial improvement or remission of suicidal ideation and impulses for the majority of patients; SSRIs were thought to potentially "carry a lower risk for suicide than older tricyclic antidepressants" (p. 181) when taken in overdose. Furthermore, the task force stated that no evidence indicated that SSRIs triggered emergent suicidal ideation above base rates associated with depression. In addition, Warshaw and Keller (1996) determined that fluoxetine use did not increase the rate of suicide in a group of 654 patients with anxiety disorders. In a large retrospective review of patients receiving one or more of 10 antidepressants (including fluoxetine), Jick *et al.* (1995) concluded that the risk for suicide was similar among all agents.

Concern about suicidality surged in 2003, after the industry alerted the FDA that there might be an increased risk of suicide-related adverse events in children treated with paroxetine. In its review of available data, the FDA found that approximately 4% of children taking SSRIs reported or exhibited suicidal thinking or behavior (including suicide attempts)--twice the rate of those taking placebo. No completed suicides occurred among nearly 2,200 children treated with SSRIs, however.

The FDA's review was followed by a number of other studies examining this issue, including a meta-analysis of 24 pediatric trials of nine antidepressant drugs (Hammad *et al.* 2006). The authors found a modestly increased risk of suicidality (risk ratio, 1.66) for SSRIs in antidepressant trials (95% CI, 1.02-2.68). This risk must be balanced against the benefit experienced by most patients with depression when they are given antidepressant therapy. In most cases, the therapeutic benefit of SSRIs will outweigh the risk of increased suicidal thoughts or behaviors (Bridge *et al.* 2007).

Black box warning. On March 22, 2004, the FDA issued a public health advisory warning of the risk of worsened depression and suicidality in children and adolescents being treated with antidepressant medications (Krause and Mehlinger 2005). This was followed by placement of a black box warning on the packaging of all antidepressant

medications, which was revised in 2006 to include adults through age 25 years. After the black box warning was placed, prescriptions for antidepressants decreased and suicide attempts in children and adolescents increased (Lu *et al.* 2014). A review of studies claiming that the black box warning led to more youth suicides concluded that these studies were methodologically weak and that the warning "is firmly rooted in solid data" (Spielmans *et al.* 2020). A commentary on this review suggested that the increased risk may have to do with incomplete maturation of the youthful brain. The commentary also noted that although the benefits of antidepressants outweigh the risks "for the majority of these patients . . . prescribers have a 'duty to warn' " (Goodman and Storch 2020).

Selective Serotonin Reuptake Inhibitor Discontinuation Syndrome

Discontinuation symptoms have been described with several classes of antidepressants. SSRI discontinuation symptoms have been reported least frequently with fluoxetine, mostly likely because of the long elimination half-lives of the parent compound and active metabolite (Haddad 1997; M.

M. S. Stahl *et al.* 1997). The most common physical symptoms are dizziness, nausea, vomiting, fatigue, lethargy, flulike symptoms (e.g., aches and chills), and sensory (e.g., paresthesia) and sleep disturbances. The most commonly reported psychological symptoms are anxiety, irritability, and crying spells. For most patients, the discontinuation symptoms are different from the adverse effects that they may have experienced while taking an SSRI. Discontinuation symptoms most often emerge within 1-3 days (Schatzberg *et al.* 1997).

Rosenbaum *et al.* (1998) compared the effects of a 5-to 8-day abrupt discontinuation period from fluoxetine, paroxetine, or sertraline in three groups of patients with depression receiving maintenance therapy. Patients in the paroxetine and sertraline groups had a significant increase in adverse events, whereas those in the fluoxetine group experienced no increase.

Consequently, SSRIs with short half-lives (paroxetine, citalopram, escitalopram, fluvoxamine) and related drugs, such as venlafaxine, should be tapered. Fluoxetine usually does not require tapering, given that plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which reduces the risk of discontinuation symptoms. However, if intolerable discontinuation symptoms do occur, resuming the previously prescribed dosage followed by a gradual dosage taper may be considered (Eli Lilly 1987).

Overdose

A major advantage of SSRIs has been their superior therapeutic index (Cooper 1988; Pedersen *et al.* 1982). The number of deaths per 1 million prescriptions across several SSRIs (range, 0-6) is substantially lower than that for conventional TCAs (range, 8-53) or MAOIs (range, 0-61) (Leonard 1992).

Borys *et al.* (1992) reported on 234 cases of fluoxetine overdose (serum level of 232-1,390 ng/mL). Fluoxetine was the sole ingestant in 87 cases; in the remaining 147 cases, it was taken in combination with alcohol and/or other drugs. Common symptoms included tachycardia, sedation, tremor, nausea, and emesis. The authors concluded that the emergent symptoms were minor and of short duration; thus, aggressive supportive care "is the only intervention necessary" (Borys *et al.* 1992, p. 115).

Drug-Drug Interactions

SSRIs are unlikely to be associated with many of the problems seen with the earlier antidepressants, including the cumulative CNS-depressant effects with alcohol, anticholinergic agents, or antihistaminic compounds. One potential for clinically relevant SSRI pharmacokinetic interactions is based on the drug effect on the CYP family of enzymes (Brosen and Gram 1989). For example, SSRIs are both substrates for and inhibitors of oxidation via CYP2D6. Crewe *et al.* (1992) ranked the potency of CYP2D6 inhibition for serotonergic antidepressants, revealing the most clinically relevant effects on CYP2D6 for paroxetine and fluoxetine.

Through inhibition of CYP2D6, fluoxetine may elevate the concentration of concomitantly administered drugs that rely on this enzyme for metabolism. This has particular clinical relevance when the second agent has a narrow therapeutic index. Examples of such agents include TCAs, several antipsychotics (particularly thioridazine, haloperidol, and clozapine), alprazolam, carbamazepine, flecainide, phenytoin, haloperidol, clozapine, quinidine, and propafenone (Rudorfer and Potter 1989), as well as other drugs metabolized by CYP2D6. The clinical consequence of such an interaction may either enhance or impair efficacy and/or heighten the adverse event profile. Fluoxetine should be used with caution in combination with drugs that cause QT prolongation, such as antibiotics (e.g., erythromycin and moxifloxacin), antiarrhythmic medications (e.g., quinidine and sotalol), and others (e.g., methadone, mefloquine, and tacrolimus).

The data with respect to fluoxetine's inhibition of other CYP enzymes, such as CYP3A3/4, CYP2C9, and CYP2C19, are less consistent, but the potential for such interaction exists.

Use in Pregnancy and Lactation

Published information about the use and safety of SSRIs in pregnancy and lactation is evolving. Goldstein *et al.* (1997) evaluated the outcomes of 796 prospectively identified pregnancies with confirmed first-trimester exposure to fluoxetine. Historical reports of newborn surveys were used for comparison. Abnormalities were observed in 5% of the fluoxetine-exposed newborns, which was consistent with rates in historical control subjects. In a review of studies published through 2012, the authors concluded that the small increase in the reported risk of cardiovascular malformation associated with fluoxetine in pregnancy was most likely attributable to ascertainment bias (Riggin *et al.* 2013). To aid in decision-making, Alwan *et al.* (2016) recommended offering ultrasound and fetal electrocardiography to all pregnant women taking an SSRI. In a 2017 review of the literature from 2005 to 2015 concerning psychopharmacotherapy in pregnancy and breastfeeding, the authors concluded that fluoxetine did not increase the risk of congenital malformations (Vitale *et al.* 2016). In a contemporaneous study of 16 cohort studies, Gao *et al.* (2017) concluded to the contrary that fluoxetine use during the first trimester was associated with "a slightly increased risk of cardiovascular malformations." However, investigators in a study of a large cohort of women exposed to an antidepressant in the year before pregnancy or during pregnancy found no increase in risk for major congenital malformation in the infants of those exposed to fluoxetine (Berard *et al.* 2017). An earlier review of the literature showed a statistically increased risk of persistent pulmonary hypertension of the newborn for infants exposed to SSRIs in late pregnancy, although clinically the absolute risk was low (Grigoriadis *et al.* 2014). The authors of a subsequent review agreed, but noted that rates of cardiovascular malformations did not differ from those seen in pregnancies of groups of mothers with depression or anxiety (Bandoli *et al.* 2020). In a review of meta-analyses of SSRI use in pregnancy, Uguz (2020) concluded, on the other hand, that the data consistently suggest that fluoxetine is associated with an increased risk of major congenital abnormalities. Given these varying reports, deriving in part from limited sample sizes, Dublin *et al.* (2020) called for new approaches to studying medication safety in pregnancy, including increased resources and collaborations that create larger databases to increase statistical power and the ability to reliably evaluate risks associated with individual drugs.

A longitudinal observational study reported no differences in growth variables (weight, length, and head circumference) from birth to age 12 months between infants exposed to SSRIs and those not exposed (Wisner *et al.* 2013). Pregnancy outcomes and follow-up cognitive and behavioral assessments for 135 children exposed in utero to a TCA or fluoxetine (55 infants) were compared with those for children in a control group of mother-infant pairs (Nulman *et al.* 1997). The incidence of major malformations and perinatal complications was similar among the three groups. No statistically significant differences in mean global IQ scores or language development were found in the children of mothers who received a TCA or fluoxetine compared with the children of control mothers. There were also no differences among the groups on several behavioral assessments. The results of children exposed during the first trimester were not different from those of children exposed throughout the pregnancy. A study failed to find a significant association between risk of autism spectrum disorder in offspring and maternal use of SSRIs--including fluoxetine--during pregnancy (Hviid *et al.* 2013).

Fluoxetine is secreted into breast milk (Hendrick *et al.* 2001). However, exposure of breastfeeding infants to fluoxetine is minimal, given the low concentrations and other factors, so the implications of this finding are unclear. Most of the available data (Burch and Wells 1992; Isenberg 1990; Taddio *et al.* 1996) suggested no adverse effects in exposed infants over the short period they were followed.

For women with depression responding to fluoxetine, the risks of discontinuing this medication or switching to a different antidepressant should be weighed against the risks of continuation. Risks associated with discontinuation include preterm birth, increased suicide attempts, decreased adherence to medical treatments, and decreased ability to care for the newborn.

Summary for Fluoxetine

Fluoxetine has been shown to be better tolerated than TCAs and to have a superior safety profile in overdose. Evidence suggests broad efficacy for fluoxetine across a spectrum of psychopathology.

Fluvoxamine

Fluvoxamine is a member of the SSRI family of drugs. This medication was initially manufactured in the United Kingdom in 1971. Fluvoxamine was registered as an antidepressant in Switzerland in 1983, becoming the first drug in the SSRI class to reach the market. Since its introduction, fluvoxamine has undergone a wide range of efficacy trials in depression, several anxiety disorders, and OCD. Fluvoxamine has been available in the United States since 1994, when the FDA approved it for the treatment of OCD (Ware 1997).

Structure-Activity Relations

Fluvoxamine belongs to the 2-aminoethyl oxime ethers of the aralkyl ketones (Figure 12-2) and is chemically identified as 5-methoxy-4'-(trifluoromethyl) valerophenone-(E)-O-(2-aminoethyl) oxime maleate (1:1). Fluvoxamine's empirical formula is $C_{15}H_{21}O_2N_2F_3*C_4H_4O_4$, and it does not have a chiral center or exist in stereoisomers. Because of local irritant properties, fluvoxamine cannot be administered parenterally (Physicians' Desk Reference 2015).

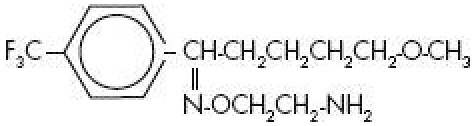

FIGURE 12-2. Chemical structure of fluvoxamine.

Mechanism of Action

Like other SSRIs, fluvoxamine binds to the presynaptic SERT and prevents it from reabsorbing serotonin into the presynaptic terminals, which increases the amount of serotonin in the synaptic cleft. How this translates into efficacy has been hypothesized to involve 5-HT_{1A} autoreceptor desensitization (Stahl 1998), increased sensitivity of $dopamine_2$-like receptors in the nucleus accumbens (Gershon *et al.* 2007), enhanced neurogenesis (Dranovsky and Hen 2006), changes in mitochondrial adenosine triphosphate levels (Ferreira *et al.* 2014), and individual pharmacogenomics factors involving SERT and catechol O-methyltransferase gene variants (Fukui *et al.* 2014; Mancama and Kerwin 2003). Furthermore, sigma-1 receptors seem to modulate several neurotransmitter pathways, and evidence suggests that fluvoxamine's affinity for the sigma-1 receptor exceeds that of all other SSRIs (Ishikawa *et al.* 2007).

Like fluoxetine, fluvoxamine's mechanism of action may involve its ability to bind to the transmembrane domain of tyrosine kinase receptor 2 (TRKB) to promote TRKB stimulation of BDNF-induced neuronal plasticity and circuit rewiring (Hashimoto 2013).

Pharmacological Profile

Fluvoxamine is a more potent inhibitor of serotonin reuptake than the TCAs, including clomipramine, but is less potent than the other SSRIs. It is highly selective for the serotonin transporter (inhibition constant $[K_i] = 2.3$ nmol/L) and has minimal affinity for the norepinephrine and dopamine transporters or the muscarinic, a_1-adrenergic, histaminic, and serotonin$_{2C}$ receptors. It possesses no MAO-inhibiting properties (Lapierre *et al.* 1983; Owens *et al.* 2001; Palmer and Benfield 1994; Ware 1997).

Formulations

In the United States, fluvoxamine formulations include immediate-release tablets and extended-release capsules in multiple strengths (U.S. Food and Drug Administration 2023).

Pharmacokinetics and Disposition

Fluvoxamine is almost entirely absorbed from the gastrointestinal tract, regardless of the presence of food (van Harten 1995). Still, first-pass metabolism limits oral bioavailability to 53% (DeVane 2003; DeVane and Gill 1997). Peak plasma concentrations occur within 2-8 hours, and steady-state concentration is achieved within 10 days (van Harten 1995). Plasma concentration shows no consistent correlation with efficacy or side effects, limiting the value of monitoring concentration.

The mean half-life of fluvoxamine is 15 hours, making twice-daily dosing preferable. Despite fluvoxamine's relatively short half-life, discontinuation syndrome is rare (Buchberger and Wagner 2002), possibly because of the drug's slower elimination from the brain (Strauss *et al.* 1998).

Because fluvoxamine is widely distributed and reaches higher concentrations in the brain and other organs than in plasma (Benfield and Ward 1986), patients receiving hemodialysis do not require replacement dosages; reequilibration should occur (DeVane and Gill 1997).

Compared with other SSRIs, fluvoxamine's rate of protein binding is relatively low (77%) (DeVane and Gill 1997), implying less risk of interactions from drug displacement.

At least 11 products of fluvoxamine metabolism are known, but none seem pharmacologically active (DeVane and Gill 1997; Palmer and Benfield 1994). Metabolism is thought to occur primarily through oxidative demethylation. Only minimal amounts of fluvoxamine (3%) are excreted unchanged by the kidneys (van Harten 1995).

Because hepatic clearance is decreased in elderly persons and individuals with liver disease, dosage adjustments may be necessary (DeVane and Gill 1997; van Harten *et al.* 1993). No biological sex-based differences in concentration seem to exist in adults (DeVane and Gill 1997). Studies in children report a higher area under the curve than in adolescents, especially in female individuals, suggesting that lower dosages may be sufficient. No appreciable pharmacokinetic differences between adolescents and adults have been observed (Physicians' Desk Reference 2015).

Indications and Efficacy

Depression

The first trial of fluvoxamine treatment for depression occurred in 1976. Since then, several single-or double-blind RCTs have tested fluvoxamine's antidepressant efficacy against placebo, SSRIs, serotonin-norepinephrine reuptake inhibitors, TCAs, tetracyclic antidepressants, and a reversible MAOI. Although the trials varied in design, the results taken together support the efficacy and safety of fluvoxamine in treating depression (including psychotic depression) across all age groups (Fukuchi and Kanemoto 2002; Haffmans *et al.* 1996; Kiev and Feiger 1997; Otsubo *et al.* 2005; Rapaport *et al.* 1996; Rossini *et al.* 2005; Ware 1997; Zanardi *et al.* 2000; Zohar *et al.* 2003).

Study durations ranged from 4 to 7 weeks, and dosages ranged from 50 to 300 mg/day. Furthermore, benefits from fluvoxamine seem to be sustained over at least 1 year (Terra and Montgomery 1998).

In an analysis of 54 RCTs ($N = 5{,}122$), researchers found no strong evidence to indicate that fluvoxamine was either superior or inferior to other antidepressants regarding response and remission (Omori *et al.* 2010). However, nausea and vomiting were reported more frequently with fluvoxamine compared with some other antidepressants.

Finally, because of its potent sigma-1 receptor agonism and the putative antipsychotic property such action might confer, it has been suggested that fluvoxamine monotherapy might be useful in treating psychotic depression (Furuse and Hashimoto 2009).

Panic Disorder

The largest double-blind RCT of fluvoxamine in panic disorder to date involved 188 participants assigned to 8 weeks of fluvoxamine treatment (100-300 mg/day) or placebo. At study end, significantly more individuals in the fluvoxamine group were free from panic attacks (69% vs. 46%; $P = 0.002$) (Figgitt and McClellan 2000).

Limited data suggest similar efficacy for fluvoxamine and the TCA imipramine as well as a possible potentiating effect of fluvoxamine when combined with cognitive or exposure therapy (Figgitt and McClellan 2000).

Social Anxiety Disorder

Liu *et al.* (2018) performed a meta-analysis of five RCTs that tested fluvoxamine in social anxiety disorder. They found significantly greater mean changes in Liebowitz Social Anxiety Scale scores (mean difference, 11.90; 95% CI, 8.09-15.71; $P < 0.001$) and Clinical Global Impression Scale severity of illness scores (mean difference, 0.52; 95% CI, 0.33-0.72; $P < 0.001$) among participants assigned to fluvoxamine compared with placebo, but with a higher incidence of treatment-emergent adverse events (OR, 2.66) (Liu *et al.* 2018).

Obsessive-Compulsive and Related Disorders

Obsessive-compulsive disorder in adults. The first formal test of fluvoxamine in OCD occurred in 1987 (Price *et al.* 1987). Since then, multiple randomized studies have established fluvoxamine's efficacy and safety in treating OCD. These trials have compared fluvoxamine with placebo, clomipramine, and other SSRIs.

In randomized double-blind comparisons with placebo, participants were given fluvoxamine 100-300 mg/day for 6-10 weeks. Significant improvements in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores were observed, and response rates ranged from 38% to 52% for fluvoxamine versus 0% to 18% for placebo (Figgitt and McClellan 2000).

Five double-blind comparisons of fluvoxamine and clomipramine, both dosed at 300 mg/day or less (Figgitt and McClellan 2000; Freeman *et al.* 1994; Koran *et al.* 1996; Milanfranchi *et al.* 1997; Mundo *et al.* 2000, 2001), demonstrated equal efficacy, with response rates of 56%-85% for fluvoxamine and 53%-83% for clomipramine. The results of a 10-week single-blind study of 30 participants randomly assigned to fluvoxamine, paroxetine, or citalopram suggested similar efficacy (Mundo *et al.* 1997).

Long-term maintenance treatment with fluvoxamine seems to protect against relapse. In a 2-year open-label follow-up study, Ravizza *et al.* (1996) enrolled 130 individuals who had responded to fluvoxamine 300 mg/day, clomipramine 150 mg/day, or fluoxetine 40 mg/day. Maintenance treatment at full or half dosages was significantly superior in preventing relapse compared with treatment discontinuation (Ravizza *et al.* 1996).

Predictors of response to fluvoxamine in OCD were evaluated in a study involving 17 individuals who underwent functional MRI at baseline and after 12 weeks of treatment (final dosage, 200 mg/day). Pretreatment hyperactivation of the right cerebellum and left superior temporal gyrus was associated with reduced Y-BOCS scores posttreatment (Sanematsu *et al.* 2010).

Another study investigated treatment compliance with fluvoxamine and cognitive therapy. Forty-eight individuals with OCD who did not respond to behavioral therapy were randomly assigned to 12 weeks of either fluvoxamine ($n = 26$) or cognitive therapy ($n = 22$). Although a higher baseline Y-BOCS score and assignment to cognitive therapy were associated with better compliance, the fluvoxamine group demonstrated statistically superior improvement compared with the cognitive therapy group (Landsheer *et al.* 2015).

In a recent study, Zheng *et al.* (2019) tested augmentation with methylphenidate as a means of improving response to fluvoxamine in OCD. Forty-four participants were randomly assigned to fluvoxamine (250 mg/day) given with extended-release methylphenidate (36 mg/day) or with placebo. A significantly higher reduction in Y-BOCS score was seen for the fluvoxamine group ($P < 0.001$) (Zheng *et al.* 2019).

Obsessive-compulsive disorder in children and adolescents. Fluvoxamine (50-200 mg/day) was tested in a 10-week, double-blind, placebo-controlled study involving 120 participants ages 8-17 years with OCD. Response was defined as a reduction of at least 25% in Children's Y-BOCS scores. Mean scores were significantly lower in the fluvoxamine group as early as week 1 ($P < 0.05$). End-of-study response rates were 42% for the fluvoxamine group and 26% for the placebo group ($P = 0.065$). The most common side effects were insomnia and asthenia (Riddle *et al.* 2001).

Other obsessive-compulsive and related disorders. Three open-label trials of fluvoxamine involving a total of 75 participants with body dysmorphic disorder reported response rates of 63%-67% (Perugi *et al.* 1996; Phillips *et al.* 1998, 2001). A 12-week open-label study of fluvoxamine administered to 21 participants with trichotillomania produced only minor improvement (Stanley *et al.* 1997).

Other addictive or impulse-control disorders. Like other SSRIs, fluvoxamine has produced inconsistent results when tested in impulse-control disorders or behavioral addictions that are sometimes considered part of the obsessive-compulsive spectrum. Despite encouraging open-label data for individuals with compulsive buying disorder (Black *et al.* 1997), two double-blind, placebo-controlled studies failed to show benefit over placebo (Black *et al.* 2000; Ninan *et al.* 2000).

Similarly, two small studies of pathological gambling (DSM-IV [American Psychiatric Association 1994]) suggested that fluvoxamine might be beneficial (Hollander *et al.* 1998, 2000). However, a larger 6-month double-blind, placebo-controlled study failed to show separation from placebo (Blanco *et al.* 2002).

Posttraumatic Stress Disorder

Small open-label studies suggest a role for fluvoxamine in treating PTSD (Davidson *et al.* 1998; Figgitt and McClellan 2000; Marmar *et al.* 1996; Tucker *et al.* 2000). Twenty-four Dutch World War II veterans with chronic PTSD showed significant improvement on a PTSD self-rating scale after a 12-week course of fluvoxamine (300 mg/day or less; $P = 0.04$; De Boer *et al.* 1992). More recently, a 14-week open-label trial of fluvoxamine (100-300 mg/day) in 15 U.S. veterans with combat-related PTSD reported a statistically significant decrease in Clinician-Administered PTSD Scale total scores ($P < 0.001$) (Escalona *et al.* 2002).

Eating Disorders

In a study by Fichter *et al.* (1996), 72 individuals with bulimia nervosa who had been treated successfully with psychotherapy were randomly assigned to fluvoxamine (100-300 mg/day) or placebo and were followed for 12 weeks. Fluvoxamine was significantly superior in preventing relapse ($P < 0.05$) (Fichter *et al.* 1996). The results of a small 12-week double-blind, placebo-controlled study in 12 individuals with acute bulimia nervosa suggested that fluvoxamine 200 mg/day was superior to placebo (Milano *et al.* 2005).

In a 9-week double-blind, placebo-controlled study by Hudson *et al.* (1998) in 85 individuals with binge-eating disorder, the investigators found that fluvoxamine (50-300 mg/day) was significantly more effective than placebo in reducing binge frequency.

Delirium

Antipsychotic drugs have been widely used for treating delirium but are associated with sedation, extrapyramidal side effects, and cardiac arrhythmias. Furthermore, there is an elevated risk of mortality in older patients treated with atypical antipsychotics. The endoplasmic reticulum protein sigma-1 receptors are thought to play an important role in calcium signaling and cell survival, and they may regulate a number of neurotransmitter systems implicated in the pathophysiology of delirium. Preliminary studies suggested that fluvoxamine may be effective in treating delirium because of its sigma-1 receptor effects (Furuse and Hashimoto 2010a, 2010b, 2010c; Hashimoto 2015).

Pain

Preliminary research has explored the potential antipain properties of fluvoxamine. In an RCT of 120 individuals with cancer accompanied by moderate to severe pain, participants were assigned to flexibly dosed extended-release oxycodone either alone (*n* = 60) or in combination with fluvoxamine (150 mg/day or greater; *n* = 60). Individuals in the oxycodone-only group required maximum dosages of extended-release oxycodone at 54 and 132 mg/day for moderate and severe pain, respectively, compared with 44.7 and 110 mg/day for the combination group. Participants who received fluvoxamine augmentation required lower dosages of oxycodone, but the difference was statistically significant only for severe pain (Xiao *et al.* 2014).

COVID-19

Fluvoxamine stimulates the sigma-1 receptor involved in regulating cytokine production. A review of clinical trials concluded that fluvoxamine produces a clinically meaningful and statistically significant reduction in COVID-19-related morbidity and possibly mortality (Lenze *et al.* 2023). The review noted that observational studies suggested (but did not prove) that fluoxetine and other SSRIs also reduce COVID morbidity and mortality. The authors reported that psychotropic medications including fluoxetine and fluvoxamine are under study as anticancer drugs, and--as a result of their anti-inflammatory function--may prove useful in Alzheimer's disease and other neurodegenerative disorders, CNS amyloid deposition, macular degeneration, and other disorders involving inflammatory pathophysiology.

Side Effects and Toxicology

Data from 34,587 patients enrolled in postmarketing fluvoxamine studies were combined in a database to assess safety. Dosages ranged from 50 to 300 mg/day taken over 4-52 weeks (Wagner *et al.* 1994). Overall, 14% of participants discontinued treatment because of side effects--most frequently, nausea and vomiting (4.6% and 1.7%, respectively). The adverse events reported at greater than 5% incidence were nausea, somnolence, and asthenia (15.7%, 6.4%, and 5.1%, respectively). The rate of weight gain was only 1%. Sexual side effects were not mentioned (only side effects with greater than 1% incidence were listed), although a separate open-label study designed to assess SSRI-induced sexual dysfunction in men and women showed statistically similar rates for fluvoxamine, fluoxetine, sertraline, and paroxetine (range, 54.4%-64.7%) (Montejo-Gonzalez *et al.* 1997).

Another postmarketing surveillance review covering 17 years (Buchberger and Wagner 2002) analyzed 6,658 individual reports, including 16,110 adverse drug reactions. The frequency of death was calculated at 0.9 per 100,000 patients. Suicide, mostly by overdose, was the cause of death in nearly half, but only 1.2% of overdoses involved fluvoxamine alone. Drug interactions were reported at a rate of 0.85 cases per 100,000 patients, most commonly with clozapine. Cases of switch to mania and discontinuation syndrome were also rare, occurring at rates of 0.47 and 0.38 events per 100,000 patients, respectively. Serotonin syndrome was even less frequent.

A more recent study assessed the cardiac effects of fluvoxamine in beagle dogs (*n* = 4). Dogs were administered fluvoxamine 0.1 mg/kg intravenously, corresponding to the recommended daily oral dose, followed by second and third doses of 1 and 10 mg/kg, respectively. Both supratherapeutic doses were associated with QT interval prolongation (Yamazaki-Hashimoto *et al.* 2015).

In two studies, researchers found no consistent treatment-related changes in laboratory values or vital signs in fluvoxamine-exposed subjects (Wagner *et al.* 1994).

Liver test abnormalities have been reported to occur for up to 1% of patients taking fluvoxamine; the elevations are typically modest and discontinuation is not required (LiverTox 2023).

Drug-Drug Interactions

Fluvoxamine is a potent inhibitor of CYP1A2. Drugs partially metabolized by CYP1A2 whose levels may rise as a result of fluvoxamine's inhibition of this isozyme include tizanidine, tertiary-amine TCAs (imipramine, amitriptyline, and clomipramine), clozapine, tacrine, theophylline, propranolol, and caffeine. Dosages of theophylline and clozapine should be reduced if coadministered with fluvoxamine (DeVane and Gill 1997). Conversely, a review of data from 241 patients suggests that fluvoxamine coadministration can increase the probability of antipsychotic response in individuals who cannot achieve sufficient clozapine plasma levels (Polcwiartek and Nielsen 2016).

Fluvoxamine also inhibits CYP2C19 and CYP3A4. CYP2C19 metabolizes warfarin, and elevations in warfarin concentration have been reported in patients taking fluvoxamine. As a result, closer monitoring of anticoagulation status is indicated for these patients. Alprazolam and diazepam are metabolized in part through CYP3A4, and fluvoxamine has been shown to prolong their elimination (DeVane and Gill 1997). Carbamazepine is partially metabolized through CYP3A4, and elevated carbamazepine levels have been documented in patients concomitantly taking fluvoxamine (Palmer and Benfield 1994). Other drugs whose metabolism through CYP3A4 may be affected by fluvoxamine include pimozide, methadone, and thioridazine. Because of the serious QT interval prolongation that can occur when terfenadine or astemizole is combined with the potent CYP3A4 inhibitor ketoconazole, it is recommended that fluvoxamine be avoided in patients who require these antihistamines (DeVane and Gill 1997). Of note, terfenadine and astemizole are no longer commercially available in the United States (U.S. Food and Drug Administration 2023). Fluvoxamine is contraindicated for use with thioridazine, tizanidine, pimozide, alosetron, ramelteon, and MAOIs (Jazz Pharmaceuticals 2011).

Fluvoxamine drug interactions have also been reported with sumatriptan, tacrine, tryptophan, diltiazem, propranolol, and metoprolol (Jazz Pharmaceuticals 2011).

Use in Pregnancy and Lactation

Limited data are available to guide clinicians and patients on the use of fluvoxamine in pregnancy. One study aimed to assess teratogenic or perinatal effects relating to fluvoxamine exposure in utero in 92 pregnant women, 37 of whom were taking other medications concomitantly. No significant difference in adverse events was seen in the treatment group compared with the control group (Gentile 2005). The FDA lists fluvoxamine in Pregnancy Category C.

Very limited information is available on infants exposed to fluvoxamine during lactation (Gentile 2005). In the eight cases published, no adverse events were reported.

Summary for Fluvoxamine

Nearly four decades of research have established fluvoxamine as a generally well-tolerated medication with potential efficacy across a range of disorders. However, two factors may have prevented even more widespread use: drug-drug interactions, which make fluvoxamine a less attractive choice for some patients, and a perception, especially in the United States, that fluvoxamine is primarily an anti-OCD drug.

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CHAPTER 13

Sertraline and Paroxetine

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Sertraline and paroxetine are classified as selective serotonin reuptake inhibitors (SSRIs) because of their potent inhibition of presynaptic serotonin uptake. Initially approved for depression, both medications have proven effective for a wide array of psychiatric disorders. Sertraline has received FDA approval for the treatment of depression, OCD (adult and pediatric populations), PTSD, panic disorder, premenstrual dysphoric disorder, and social anxiety disorder. Paroxetine has received FDA approval for depression, panic disorder, social anxiety disorder, generalized anxiety disorder, OCD, PTSD, premenstrual dysphoric disorder, and vasomotor symptoms (hot flashes) associated with menopause. Like other SSRIs, sertraline and paroxetine are characterized by good tolerability profiles, increasing their usefulness in comparison with older antidepressants.

History and Discovery

The synthesis of the first SSRI, fluoxetine, in 1972 marked the inception of an exciting new era of scientific and clinical innovation in psychiatry (Wong *et al.* 1995). Prior to this discovery, psychiatrists had only a few classes of pharmacological treatments for managing depression and anxiety. These medication classes, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and benzodiazepines, were indeed efficacious; however, they were poorly tolerated and therefore quite limited in usefulness.

Shortly after the introduction of fluoxetine into the U.S. market in 1988, a marked increase in research led to the development of other SSRIs, which ultimately proved effective in a wide array of psychiatric disorders. In 1991, sertraline became the second SSRI to be approved by the FDA for the treatment of depression; the following year, paroxetine became the third SSRI to receive approval.

Sertraline is marketed as immediate-release tablets, higher-strength capsules, and an oral solution concentrate. Generic equivalent products are available for most dosage forms. The oral solution has been shown to be bioequivalent to the 20-mg tablet and may be useful for ease of administration and for tapering dosages of sertraline (van den Tweel *et al.* 2007). Paroxetine hydrochloride, originally marketed under the name Paxil, is available as immediate-release tablets, controlled-release tablets, and an oral suspension. Generic products are available for these dosage forms. Paroxetine is also marketed in a mesylate salt form as tablets and in a capsule formulation. These products are discussed in greater detail later in the chapter.

Structure-Activity Relations and Pharmacological Profile

Sertraline (Figure 13-1) and paroxetine (Figure 13-2) specifically block the reuptake of serotonin in the soma and terminal regions of serotonergic neurons. Serotonin neurons in the midbrain raphe nuclei have inhibitory autoreceptors in both the soma (serotonin$_{1A}$ [5-HT$_{1A}$] receptors) and terminal area (serotonin$_{1B}$ receptors) that are stimulated by the acute increase in serotonin. The immediate effect of serotonin transporter (5-HTT) blockade is to increase the amount of serotonin in axosomatic synapses and to decrease neuronal firing (Blier 2001; Blier *et al.* 1990;

Heym and Koe 1988). Over several weeks, these autoreceptors are desensitized and firing rates increase.

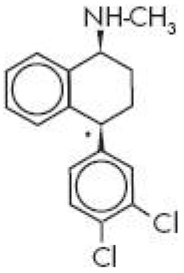

FIGURE 13-1. Chemical structure of sertraline.

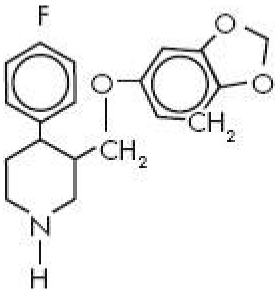

FIGURE 13-2. Chemical structure of paroxetine.

Among the various antidepressant agents that block 5-HTT, paroxetine and sertraline are the highest and second highest, respectively, in potency for serotonin reuptake blockade, as demonstrated in animal models (Hiemke and Hartter 2000; Owens *et al.* 2001; Richelson 1994). The selectivity of sertraline for norepinephrine follows that of escitalopram (Hiemke and Hartter 2000; Owens *et al.* 2001), although other work suggests greater selectivity for fluvoxamine than for sertraline (Richelson 1994). In contrast, paroxetine is the most potent inhibitor of the norepinephrine transporter among drugs classified as SSRIs, although paroxetine's norepinephrine transporter antagonism does not approach the magnitude of its 5-HTT antagonism (Finley 1994). Substantial norepinephrine transporter antagonism does occur at dosages of 40 mg/day

or greater for immediate-release paroxetine (Gilmor *et al.* 2002). The relative selectivity for 5-HTT, compared with the dopamine transporter, is lowest for sertraline, whereas paroxetine has low affinity for the dopamine transporter (Owens *et al.* 2001).

While sertraline has little appreciable antagonistic effect on muscarinic cholinergic receptors, the affinity of paroxetine for the muscarinic cholinergic receptor is similar to that of desipramine. Paroxetine is used at lower dosages than desipramine and is therefore less anticholinergic than this tricyclic agent. However, this property may account for paroxetine's mild anticholinergic side effects, including dry mouth, blurry vision, and constipation (Owens *et al.* 1997). Neither sertraline nor paroxetine exhibits appreciable affinity for histamine$_1$ receptors (Hiemke and Hartter 2000; Richelson 1994). The antagonism of a$_1$ adrenoreceptors by sertraline is at least 10-fold more potent than that of other SSRIs (Hiemke and Hartter 2000), although this antagonism does not translate into clinically meaningful hypotension or reflex tachycardia. However, a previous report suggested that sertraline decreases sympathetic nervous system activity, a property consistent with receptor blockade (Shores *et al.* 2001). It is also possible that the decrease in sympathetic response is related to stimulation of the 5-HT$_{1A}$ receptors noted earlier.

Sertraline is metabolized to desmethylsertraline (see the following section, "Pharmacokinetics and Disposition"). This compound is approximately one-tenth as active in blocking the reuptake of serotonin; it also lacks antidepressant activity in animal models (Heym and Koe 1988).

Sertraline exhibits inhibitory activity on several cytochrome P450 (CYP) enzymes. The ability of the compound to slightly elevate dextromethorphan and desipramine supports modest inhibition of CYP2D6 (Hiemke and Hartter 2000; Ozdemir *et al.* 1998; Preskorn 1996). It has little appreciable inhibition of CYP1A2, even when used at higher dosages (Ozdemir *et al.* 1998). A very mild elevation of CYP2C9/10 substrates has been found in several studies (Preskorn 1996). Sertraline has complex effects on the CYP3A3/4 enzyme system: it initially shows slight inhibition, but it also induces this system, albeit modestly, over time (Preskorn 1996). Paroxetine is the most potent inhibitor of the CYP2D6 enzyme system among the SSRIs (Crewe *et al.* 1992; Nemeroff *et al.* 1996), and its inhibition of CYP2D6 can continue for up to 5 days after discontinuation (Liston *et al.* 2002).

Pharmacokinetics and Disposition

Absorption and Distribution

Sertraline

Sertraline is absorbed slowly via the gastrointestinal tract, with peak plasma levels occurring between 6 and 8 hours after ingestion (Warrington 1991). The delay may be the result of enterohepatic circulation (Hiemke and Hartter 2000; van Harten 1993). Sertraline tablets may be taken with or without food (Pfizer 2021). The medication is more than 95% protein bound; however, because it binds weakly to a_1 glycoproteins, it does not cause substantial displacement of other protein-bound drugs (Preskorn 1996).

The volume of distribution of sertraline is large, exceeding 20 L/kg. The distribution is larger in young (18-45 years) female individuals than in young male individuals (Warrington 1991). In animal models, the concentration of sertraline is 40 times higher in brain than in plasma (Hiemke and Hartter 2000).

Paroxetine

Paroxetine is well absorbed from the alimentary tract, and absorption is not affected by the presence or absence of food (Kaye *et al.* 1989). Paroxetine is highly lipophilic and is readily distributed into peripheral tissues, with a high volume of distribution and 95% protein binding (Kaye *et al.* 1989). Oral bioavailability is affected by extensive first-pass metabolism (Lane 1996). With serial dosing, bioavailability increases as the hepatic metabolic system becomes saturated and a larger proportion of the parent compound enters the systemic circulation (Kaye *et al.* 1989). After oral dosing, steady-state concentrations of paroxetine exhibit wide intersubject variability (Sindrup *et al.* 1992a); however, there appears to be no relationship between paroxetine levels and clinical response or adverse outcomes (Tasker *et al.* 1989).

Metabolism and Elimination

Sertraline

The elimination half-life of sertraline is 26-32 hours, and steady-state levels are achieved after 7 days. Sertraline shows linear pharmacokinetics within a range of 50-200 mg/day (Warrington 1991) and does not appear to inhibit or induce its own metabolism. Peak plasma levels are somewhat lower in young male individuals than in young female, older female, or older male individuals (Ronfeld *et al.* 1997; Warrington 1991), and the elimination rate constant is higher in young (18-45 years) male individuals (0.031/hour) than in young female (0.022/hour) and older ([?] 65 years) female or male individuals (0.019/hour). Maximal plasma concentrations of sertraline may be significantly reduced after a gastric bypass procedure (Roerig *et al.* 2012).

In children between the ages of 6 and 17 years, weight-corrected metabolism is more rapid. The maximum concentration and the area under the curve are 22% lower in children than in adults. Despite this relatively more efficient metabolism, the smaller body mass of most children suggests that lower dosages of sertraline should be used in pediatric populations (Pfizer 2021).

Sertraline is metabolized in the liver via oxidative metabolism; the concentration of the primary metabolite, desmethylsertraline, is up to threefold higher than that of the parent compound (Hiemke *et al.* 1991; Ronfeld *et al.* 1997; Warrington 1991). Desmethylsertraline levels are also lower in young male individuals than in young female, elderly female, or elderly male individuals. The peak concentration of desmethylsertraline is attained more quickly in young female individuals (6 hours) than in young male, older female, and older male individuals (9, 8, and 14 hours, respectively) (Warrington 1991). The half-life of desmethylsertraline is 1.6-2.0 times that of the parent compound (Warrington 1991).

Whereas desmethylsertraline is the major metabolite of sertraline, other minor metabolites include a ketone and an alcohol compound (Warrington 1991). Less than 0.2% of an oral dose of sertraline is excreted unchanged in urine, whereas approximately 50% is found in feces. The enzymes involved in the metabolism of sertraline to desmethylsertraline remain unclear (Greenblatt *et al.* 1999). Although six different CYP enzymes have the capacity to catalyze this reaction, none account for more than 25% of sertraline's clearance. The contribution of each CYP enzyme is dependent not only on the protein's activity on the substrate, as evidenced through in vitro models, but also on the abundance of the enzyme. Given these properties, one computer model identified CYP2C9 as the greatest contributor (approximately 23%) to sertraline demethylation, with CYP3A4 and CYP2C19 each contributing about 15%, CYP2D6 adding 5%, and CYP2B6 contributing 2% to the process (Greenblatt *et al.* 1999; Lee *et al.* 1999). These percentages can vary across individuals, depending on the amount of available enzyme or enzyme inhibition that occurs. Because multiple CYP enzymes are involved in sertraline's metabolism, concurrent use of medications with specific CYP inhibition is unlikely to substantially impair the process (Greenblatt *et al.* 1999). However, increased CYP2B6 activity was seen in mice as a consequence of sertraline coadministration with bupropion (Molnari *et al.* 2012). A more recent study from Denmark reported that CYP2C19 also contributes to sertraline blood levels, and individuals who are slow metabolizers due to allelic variation may require dosage reductions in sertraline (Braten *et al.* 2020).

Patients with liver disease experience decreased sertraline metabolism (Hiemke and Hartter 2000). For individuals with mild liver impairment, the half-life of the drug may be increased threefold (Pfizer 2021), and concentrations are likely to be greater in patients with severe impairment. Although renal impairment does not appreciably influence the metabolism of sertraline (Hiemke and Hartter 2000), patients with severe end-stage renal disease undergoing hemodialysis do not appear to tolerate sertraline 25 mg/day without risk of significant toxicity (Chander *et al.* 2011).

Paroxetine

The average elimination half-life of paroxetine is approximately 21 hours (coefficient of variation [CV], 32%). Because of paroxetine's nonlinear pharmacokinetics (discussed later in chapter), time to steady state will vary among individuals. In repeat-dose studies in healthy volunteers, steady state was achieved within 2 weeks for both the immediate-release and the controlled-release dosage forms (GlaxoSmithKline 2019).

The rate-limiting step in the metabolism of paroxetine is the CYP2D6 enzyme system (Crewe *et al.* 1992; Sindrup *et al.* 1992a). Genetic studies have demonstrated as many as 40 polymorphisms of the CYP2D6 enzyme, which in part may explain the differences in pharmacokinetic parameters observed among individuals (Lane 1996). Individuals can be categorized by CYP2D6 phenotype as being poor, intermediate, extensive, or ultrarapid metabolizers, denoting that they have very high, high, low, or very low serum paroxetine concentrations, respectively (Charlier *et al.* 2003). Ultrarapid metabolizers may be at greater risk of antidepressant nonresponse, although this has not been clearly demonstrated, and paroxetine's minimum therapeutic concentration is not well defined. Similarly, a putative increased risk of adverse events for poor metabolizers has not been confirmed (Hicks *et al.* 2015). Patients with negligible or diminished CYP2D6 activity are thought to use alternative enzyme systems (Gunasekara *et al.* 1998; Lane 1996).

Given its potent inhibition of the CYP2D6 enzyme system (Crewe *et al.* 1992; Nemeroff *et al.* 1996), paroxetine is both a substrate and inhibitor of its own metabolism. Paroxetine therefore has a nonlinear pharmacokinetic profile, such that higher dosages produce disproportionately greater plasma drug concentrations as the enzyme becomes saturated (Preskorn 1993). With immediate-release paroxetine, peak plasma concentration is attained in approximately 5 hours, and plasma steady-state concentration is achieved within 4-14 days (Kaye *et al.* 1989). The terminal half-life of the parent compound is approximately 1 day and increases at higher dosages, consequent to autoinhibition of CYP2D6 (Preskorn 1993). The pharmacokinetic properties of paroxetine appear to be affected by age. Bayer *et al.* (1989) reported a threefold increase in maximum plasma concentration in elderly persons compared with younger individuals after a single dose of paroxetine. Furthermore, the terminal half-life in the elderly subgroup was extended by nearly 100%.

In individuals with renal impairment, both half-life and maximum plasma levels of paroxetine have been shown to increase relative to the extent of kidney disease (Doyle *et al.* 1989). In patients with severe liver disease, there are considerable elevations in the steady-state concentration and the terminal half-life of paroxetine (Dalhoff *et al.* 1991). Patients with substantial renal or hepatic impairment should initially receive lower paroxetine dosages to avoid potential side effects.

The controlled-release paroxetine formulation is designed to slow absorption and delay the release of paroxetine until after the tablet has passed through the stomach. With this formulation, 20% of the drug is excreted unchanged from the gastrointestinal tract, such that 20% higher dosages of controlled-release paroxetine are necessary to achieve the same bioavailability (DeVane 2003). Dissolution after single dosing takes 4-5 hours; otherwise, controlled-release paroxetine displays the same pharmacokinetic parameters as the immediate-release formulation with regard to terminal half-life and nonlinearity.

Paroxetine mesylate is marketed as a novel 7.5-mg capsule (Brisdelle, discussed later in chapter [see subsection "Menopausal Vasomotor Symptoms"]) and as 10-mg, 20-mg, 30-mg, and 40-mg tablets. The product labeling for these tablets (Noven Therapeutics 2013) does not describe them as being bioequivalent to paroxetine hydrochloride tablets, and the FDA Orange Book (U.S. Food and Drug Administration 2023) does not list them as being bioequivalent. No studies have compared this formulation's efficacy against that of paroxetine hydrochloride, and case reports have indicated problems of decreased efficacy and poor tolerability for patients switched from paroxetine hydrochloride to paroxetine mesylate (Borgheini 2003).

Mechanism of Action

The means by which all antidepressants exert their therapeutic action are largely unknown, although some of the properties have been related to hypothetical mechanisms (Blier 2001; Blier *et al.* 1990). Sertraline, paroxetine, and all of the other SSRIs cause immediate elevations in extracellular serotonin concentrations in serotonergic synapses, resulting from the decreased serotonin clearance associated with 5-HTT inhibition (Wagstaff *et al.* 2002). SSRIs initially cause a paradoxical *decrease* in serotonin neurotransmission, likely due to activation of a negative feedback system mediated by increased serotonin binding to the 5-HT$_{1A}$ autoreceptor and subsequent diminution in serotonergic neural activity (Blier *et al.* 1990). After 2-3 weeks of treatment, the 5-HT$_{1A}$ autoreceptors are desensitized, and there is an associated increase in serotonergic neurotransmission (Blier 2001; Chaput *et al.* 1991). The delayed changes in 5-HT$_{1A}$ receptor sensitivity and serotonin neurotransmission seen after long-term use are temporally associated with clinical improvement, hinting at a possible mechanistic link. Not inconsistent with this are findings suggesting that SSRI treatment decreases production of serotonin$_{1B}$ messenger RNA, the message for a regulatory autoreceptor on dorsal raphe neurons that controls the amount of serotonin released with each impulse (Anthony *et al.* 2000). Again, the decrease in messenger RNA production coincides with the time frame for SSRI therapeutic effects.

Indications and Efficacy

Major Depressive Disorder

Sertraline

Sertraline's efficacy in the treatment of major depressive disorder (MDD) was established by a number of placebo-controlled trials for acute-phase therapy (Fabre *et al.* 1995; Olie *et al.* 1997; Reimherr *et al.* 1990). In a multicenter trial, 369 patients were randomly assigned to a fixed dosage of sertraline (50, 100, or 200 mg/day) or placebo for 6 weeks (Fabre *et al.* 1995). Patients at all dosages of sertraline showed approximately equivalent improvement, which was greater than that shown with placebo for most measures.

Sertraline was compared with amitriptyline and placebo in a multicenter trial of 448 patients (Reimherr *et al.* 1990). Sertraline was dosed flexibly up to 200 mg/day, and amitriptyline was administered at dosages as high as 150 mg/day. Both active treatments were superior to placebo, as indicated by Hamilton Rating Scale for Depression (Ham-D) and Clinical Global Impression (CGI) Scale scores; similarly, response rates (i.e., rates at which patients attained a 50% decrease in Ham-D score or a CGI score of 1 or 2) were higher with the active treatment compared with placebo.

In a multicenter study of 235 men and 400 women with either chronic MDD (enduring at least 2 years) or MDD superimposed on DSM-IV (American Psychiatric Association 1994) dysthymic disorder, participants were randomly assigned to 12 weeks of either sertraline or imipramine in a 2:1 ratio (Kornstein *et al.* 2000). Treatment was double blinded, and the study medication was titrated to a flexible maximum daily dosage of sertraline 200 mg or imipramine 300 mg. Response to both drugs was similar, but sertraline was better tolerated. The results revealed that many who benefited had not achieved response until after 8 weeks of treatment, underscoring the need for extended sertraline trials in patients with chronic depression (Keller *et al.* 1998a). Another interesting finding from this study is that men and women differed in their response to sertraline and imipramine (Kornstein *et al.* 2000). Remission and response outcomes were combined in an intent-to-treat analysis that showed that 57% of women, but only 46% of men, benefited from sertraline. Among men, response was somewhat better with imipramine than with sertraline (62% and 45%, respectively). Response was more rapid for men assigned to imipramine and for women assigned to sertraline. Among women, those who were premenopausal were more likely to respond to sertraline, whereas postmenopausal women were equally likely to respond to either agent.

Several trials have shown roughly equivalent efficacy for sertraline and other SSRIs (Aguglia *et al.* 1993; Franchini *et al.* 1997; Newhouse *et al.* 2000; Stahl 2000). However, a Cochrane Database review and meta-analysis of all randomized controlled trials of sertraline against an active antidepressant comparator concluded that sertraline was superior to other agents for the treatment of MDD in terms of both efficacy and acceptability (Cipriani *et al.* 2010).

In the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) trial on biomarker development, sertraline was not significantly more effective than placebo in MDD (Webb *et al.* 2019). However, low ventral striatal activity on functional MRI at baseline appeared to predict separation of sertraline from placebo (Greenberg *et al.* 2020). In addition, decreased irritability with treatment was associated with significant separation in overall response between sertraline and placebo in those patients (Jha *et al.* 2020).

Sertraline has been shown to be effective for maintenance-phase treatment, both for patients with MDD (Doogan and Caillard 1992) and for individuals with chronic MDD (defined as a major depressive episode enduring at least 2 years or co-occurring with dysthymic disorder) (Keller *et al.* 1998b). The Doogan and Caillard (1992) study followed 300 patients throughout 44 weeks of double-blind, placebo-controlled maintenance therapy and found that 13% of sertraline-treated patients, compared with 46% of placebo-treated patients, experienced relapse.

Keller *et al.* (1998b) examined the utility of sertraline in preventing illness recurrence among patients with chronic MDD who responded to acute antidepressant therapy (n = 161). Participants were randomly assigned to receive 52 weeks of maintenance treatment with either placebo or sertraline. More than 60% of the sample was female and had a current episode duration that exceeded 8 years. Sertraline significantly outperformed placebo on all outcome measures; 6% of sertraline-treated patients and 23% of placebo-treated patients experienced depressive episode recurrence, and clinically significant depressive symptom reemergence was observed for 26% of patients receiving sertraline versus 50% of patients receiving placebo.

Sertraline can be used to treat MDD in special populations. In addition to the trials just described, several studies found sertraline to be at least as effective as TCAs in treating younger adults (Cohn *et al.* 1990; Lydiard *et al.* 1997; Moller *et al.* 1998) and elderly patients (Bondareff *et al.* 2000; Finkel *et al.* 1999; Forlenza *et al.* 2001) with MDD. A recent small study reported that vortioxetine and sertraline were similarly effective in treating depression among elderly persons (Borhannejad *et al.* 2020). Although some studies reported that sertraline was used successfully in the treatment of children and adolescents with MDD and dysthymic disorder (Ambrosini *et al.* 1999; Nixon *et al.* 2001), a meta-analysis determined that only fluoxetine was significantly more effective than placebo for MDD in this population (Cipriani *et al.* 2016), and sertraline is not FDA approved for MDD in this age group. Sertraline has been shown to be as beneficial as nortriptyline in women with postpartum MDD (Wisner *et al.* 2006). Sertraline was significantly more effective than placebo in reducing depressive symptoms of postpartum depression (Hantsoo *et al.* 2014), particularly in women whose symptoms began within 4 weeks of giving birth. However, in another recent trial, specialized cognitive-behavioral therapy (CBT) was significantly more effective than sertraline in women with postpartum depression (Milgrom *et al.* 2015). Sertraline may confer a prophylactic advantage in women at high risk for developing postpartum episodes of MDD (Wisner *et al.* 2004), and sertraline is one of three antidepressants judged to be evidence-based choices for MDD in women who are breastfeeding (Lanza di Scalea and Wisner 2009).

Sertraline has been used to treat mood symptoms associated with a number of neurological conditions, including depression associated with Parkinson's disease (Antonini *et al.* 2006; Hauser and Zesiewicz 1997; Meara and Hobson 1998) and depression-linked fatigue in multiple sclerosis (Mohr *et al.* 2003). Sertraline also has been used to improve pathological crying and pseudobulbar-type affects (Benedek and Peterson 1995; Mukand *et al.* 1996; Okun *et al.* 2001; Peterson *et al.* 1996). In the "psychological subgroup" of a cohort of patients with Alzheimer's disease, mirtazapine, but not sertraline, separated from placebo (Zuidersma *et al.* 2019).

Sertraline is one of the few antidepressants shown to be safe for the treatment of depression in patients with cardiovascular disease. In a well-publicized study by the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group, there were no significant treatment-emergent effects of sertraline on cardiac measures (including change from baseline left ventricular ejection fraction, runs of ventricular premature complexes, or prolonged QTc intervals) (Glassman *et al.* 2002). For the entire sample, sertraline was superior to placebo in improving rates of response when defined by CGI ratings, but not when defined by Ham-D scores (Glassman *et al.* 2002). Although sertraline's safety was again demonstrated in a study of 469 SADHART patients with chronic heart failure, in this sample there was no evidence of antidepressant superiority of sertraline over placebo (O'Connor *et al.* 2010). Compared with chronic heart failure patients with nonremitting depression, those who achieved remission from depression had fewer cardiovascular events at pretreatment baseline and went on to have better cardiovascular outcomes over a 5-year period (Jiang *et al.* 2011).

Sertraline has been studied in patients with cancer and depression. A 12-week open-label, flexible-dose trial of sertraline in patients undergoing chemotherapy demonstrated positive effects on depressed mood (Torta *et al.* 2008). However, in a controlled trial of almost 200 patients with advanced disease who did not have MDD, sertraline had no mood benefit over placebo (Stockler *et al.* 2007).

Paroxetine

The efficacy of paroxetine in MDD has been established in several randomized placebo-controlled studies as well as in studies comparing the effects of paroxetine with

those of other antidepressants, including TCAs, serotonin-norepinephrine reuptake inhibitors, and other SSRIs. The earliest placebo-controlled studies used paroxetine dosages of 10-50 mg/day and were about 6 weeks in duration. A more recent meta-analysis of all published and unpublished industry-sponsored trials that included Ham-D change scores showed superiority of paroxetine over placebo, with a modest effect size of 0.32 (Sugarman *et al.* 2014). Barbui *et al.* (2008) undertook a systematic review of paroxetine, evaluating both published and unpublished data according to one specific hard measure--treatment discontinuation--by looking at the number of patients who left a study early for any reason. The authors found that when this measure was used as a primary outcome, paroxetine was not effective; when rate of response (defined as a 50% reduction or greater in Ham-D score) was used, paroxetine was superior to placebo (Barbui *et al.* 2008).

A meta-analysis by Montgomery (2001) compared the efficacy and tolerability of paroxetine with that of TCAs, including amitriptyline, imipramine, clomipramine, doxepin, and nortriptyline, as well as the tetracyclic antidepressants mianserin and maprotiline. The data demonstrated no overall significant difference in antidepressant response rates between paroxetine and TCAs or tetracyclics. However, paroxetine was better tolerated, had lower rates of discontinuation attributed to adverse events, and had a greater effect on concomitant anxiety.

Many studies have found paroxetine and fluoxetine to be equally effective in the treatment of MDD and associated anxiety (Chouinard *et al.* 1999; De Wilde *et al.* 1993; Fava *et al.* 1998, 2000; Tignol 1993). Equivalent efficacy was demonstrated in comparisons of paroxetine against either sertraline or escitalopram; however, these studies tended to also show a greater dropout rate in paroxetine groups, likely owing to adverse medication effects (Aberg-Wistedt *et al.* 2000; Baldwin *et al.* 2006; Zanardi *et al.* 1996). Some studies have suggested efficacy differences among the SSRIs, with a Cochrane Review concluding that citalopram may be superior to paroxetine in the acute phase of treatment (6-12 weeks) (Purgato *et al.* 2014).

Paroxetine has also been compared with a variety of other agents in the treatment of depression. Nefazodone and paroxetine were demonstrated to possess similar efficacy and tolerability (Baldwin *et al.* 1996), and mirtazapine and paroxetine were equivalent in terms of efficacy and tolerability (Benkert *et al.* 2000). However, in a Cochrane Review, Purgato *et al.* (2014) concluded that mirtazapine may be superior to paroxetine, whereas paroxetine may be superior to the norepinephrine reuptake inhibitor reboxetine in terms of early response to treatment (1-4 weeks). In a meta-analysis of worldwide data from studies of venlafaxine, the serotonin-norepinephrine reuptake inhibitor venlafaxine showed a slight statistically significant advantage in efficacy over SSRIs as a class, although no such advantage was demonstrated for venlafaxine over paroxetine (Nemeroff *et al.* 2003).

Studies have demonstrated the effectiveness of paroxetine in maintaining remission over an extended period without adverse effects (Duboff 1993), particularly when compared with placebo (Montgomery and Dunbar 1993). The paroxetine dosages used in the long-term studies were typically the same ones used in the acute studies (20-40 mg/day). Thus, for maintenance therapy for depression, the recommended dosage of paroxetine is the one that was effective during acute therapy.

Numerous studies have established the efficacy of paroxetine in treating depression in elderly patients (Geretsegger *et al.* 1995; Guillibert *et al.* 1989; Hutchinson *et al.* 1992; Rapaport *et al.* 2009) and for maintenance treatment in this population (Bump *et al.* 2001; Reynolds *et al.* 2006). A recent network meta-analysis determined that there is clear evidence for the effectiveness of paroxetine in depression in older adults, but paroxetine may have a greater risk of dizziness compared with placebo (Thorlund *et al.* 2015). One issue of concern in treating elderly individuals with paroxetine is the potential risk of anticholinergic side effects, leading to delirium. However, in a study comparing the effects of fluoxetine and paroxetine in depressed elderly patients without dementia, both medications produced marked improvement in cognitive functioning and mood symptoms and were well tolerated (Cassano *et al.* 2002). A meta-analysis concluded that paroxetine was not significantly associated with risk of falls in older adults (Ruxton *et al.* 2015).

Published data on paroxetine have shown limited efficacy in children and adolescents with MDD (Emslie *et al.* 2006; Keller *et al.* 2001). Paroxetine is not approved for use in pediatric patients (GlaxoSmithKline 2019). In a reanalysis of the Keller *et al.* (2001) study, Le Noury *et al.* (2015) found that the benefits of paroxetine were lower and the risks greater than had been reported in the initial publication. In particular, paroxetine did not show greater efficacy than placebo and was associated with increased risks, including suicidal ideation and behavior (Le Noury *et al.* 2015). Differences in pharmacokinetics between children and adults may explain the observed age-related discrepancies in efficacy and suicide risk. In children, an increase in dosage from 10 to 20 mg results in a sixfold increase in serum paroxetine levels (Findling *et al.* 1999). This dramatic increase in pediatric serum levels could conceivably trigger activation, akathisia, or disinhibition, potentially explaining the emergence of suicidal thinking or behavior (Brent 2004), and the effect would be even greater in children who are poor CYP2D6 metabolizers (roughly 10% of the white population) (Riddle 2004). In addition, paroxetine has a relatively short half-life (11 hours, vs. 5 days with fluoxetine), and limited treatment adherence--not uncommon in children and teens--could lead to SSRI discontinuation syndrome and dysphoria (Brent 2004).

Paroxetine is reported to be efficacious in the treatment of depression comorbid with several medical disorders, including rheumatoid arthritis, irritable bowel syndrome, cardiovascular disease, and Parkinson's disease (Bird and Broggini 2000; Masand *et al.* 2001; Richard *et al.* 2012; Roose *et al.* 1998). Along with escitalopram, paroxetine was one of the most recommended medications for poststroke depression in a recent review based on randomized controlled trials and meta-analyses (Starkstein and Hayhow 2019). However, another meta-analysis of four poststroke depression studies showed no advantage for paroxetine over placebo (Li *et al.* 2020a). Paroxetine has also been demonstrated to be efficacious in the prevention of interferon-a-induced depression in patients with malignant melanoma (Musselman *et al.* 2001).

Social Anxiety Disorder

Sertraline

Sertraline, paroxetine, controlled-release fluvoxamine, and extended-release venlafaxine are the only medications with FDA approval for the treatment of social anxiety disorder. Several studies have established the efficacy of sertraline in the treatment of social anxiety disorder. In one of the earliest studies (Katzelnick *et al.* 1995), sertraline treatment (at flexible dosages of 50-100 mg/day) produced a statistically significant improvement compared with placebo, as measured by Liebowitz Social Anxiety Scale scores. A large double-blind, placebo-controlled study followed more than 200 Canadian outpatients with generalized social anxiety disorder for 20 weeks, measuring response via CGI-Improvement (CGI-I) scores and mean reductions on the social phobia subscale of the Marks Fear Questionnaire and the Brief Social Phobia Scale (Van Ameringen *et al.* 2001). Fifty-three percent of patients treated with sertraline, compared with only 29% of patients receiving placebo, were either much or very much improved by the study's end, as measured by CGI-I scores. When patients who responded to sertraline were randomly assigned to continue sertraline or switch to placebo for an additional 24 weeks, the RR of relapse for those randomly assigned to placebo was greater than 10 (Walker *et al.* 2000).

Liebowitz *et al.* (2003) demonstrated that sertraline produced a significant reduction in Liebowitz Social Anxiety Scale scores and resulted in a greater proportion of responders after 12 weeks of treatment (at dosages up to 200 mg/day) compared with placebo. In a placebo-controlled study that compared sertraline, exposure therapy, and combined treatment and involved more than 380 Norwegian patients with generalized social anxiety disorder, sertraline alone or in combination with exposure therapy yielded statistically significant improvements in CGI social phobia scores, whereas exposure therapy alone did not (Blomhoff *et al.* 2001). Although sertraline is not FDA approved in the pediatric population, it has been well tolerated and has shown efficacy in childhood social anxiety disorder (Compton *et al.* 2001).

Paroxetine

Paroxetine's efficacy in the treatment of social anxiety disorder was first suggested by results from open clinical trials (Mancini and Van Ameringen 1996; Stein *et al.* 1996) and was later confirmed by findings from double-blind, placebo-controlled studies (Baldwin *et al.* 1999; Stein *et al.* 1998). Recent meta-analyses have also confirmed that paroxetine is effective and well tolerated for social anxiety disorder and indicate that there is more evidence for the efficacy of paroxetine than for any other agent in this class (Li *et al.* 2020b; Williams *et al.* 2020). However, a randomized controlled trial reported that cognitive therapy was more effective than either paroxetine alone or the combination of paroxetine and cognitive therapy (Nordahl *et al.* 2016).

In children and adolescents (ages 8-17 years) with social anxiety disorder, paroxetine was superior to placebo (Wagner *et al.* 2004). It is important to note that a total of five patients in the paroxetine group (*n* = 163) exhibited suicidal threats or gestures, compared with none in the placebo group (*n* = 156).

It appears that the optimal daily dosage of paroxetine for the treatment of social anxiety disorder is 20-40 mg/day, with no additional benefit seen for 60 mg/day (Lydiard and Bobes 2000). In patients who respond to paroxetine, it is also advisable to continue treatment to prevent relapse (Stein *et al.* 2002).

Panic Disorder

Sertraline

Sertraline's efficacy in the treatment of panic disorder has been demonstrated in several studies. In a 12-week randomized, placebo-controlled, flexible-dose multicenter trial in outpatients with panic disorder (with and without agoraphobia) but without

depression (Pohl *et al.* 1998), sertraline was superior to placebo on a number of efficacy measures. Patients meeting diagnostic criteria for panic disorder (*n* = 168) without depression were randomly assigned to receive sertraline or placebo after a 2-week single-blind lead in. The mean +- SD sertraline dosage at endpoint was 126 +- 62 mg/day, and the reduction in panic attack frequency was significantly greater for the sertraline group than the placebo group (77% vs. 51%), with significantly fewer panic symptom episodes occurring in that group. Similar results supporting sertraline's efficacy for panic disorder were reported by Pollack *et al.* (1998), who randomly assigned 178 patients to sertraline or placebo.

A fixed-dosage study of sertraline (50, 100, or 200 mg/day) or placebo for 12 weeks (Londborg *et al.* 1998) demonstrated sertraline's superiority over placebo in numerous trial outcomes, including the number of panic attacks and limited-symptom attacks, severity of anticipatory anxiety, dimensional anxiety measures, and global measures of improvement. Pooled sertraline data indicated a 65% reduction in the number of panic attacks, compared with a 39% decrease in the placebo group. Effect sizes, reflecting the magnitude of difference between the two treatments, for the three different sertraline dosages tested were 0.58 (50 mg/day), 0.41 (100 mg/day), and 0.60 (200 mg/day), but response rates did not differ significantly among dosage groups. In the panic studies described above (Londborg *et al.* 1998; Pohl *et al.* 1998; Pollack *et al.* (1998), the authors reported a low incidence of attrition secondary to sertraline adverse events, concluding that sertraline is a safe and effective treatment for patients with panic disorder. Sertraline's beneficial effects in panic disorder may be further enhanced when the drug is used in combination with self-administered CBT (Koszycki *et al.* 2011).

Paroxetine

Paroxetine was the first SSRI to be granted FDA approval for the treatment of panic disorder. Paroxetine and clomipramine have been shown to be equally efficacious in the treatment of panic attacks, and a faster onset of action was noted with paroxetine (Lecrubier *et al.* 1997a). Paroxetine's long-term efficacy and tolerability have also been demonstrated in patients with panic disorder (Lecrubier *et al.* 1997b; Nardi *et al.* 2012). The combination of CBT and paroxetine is more effective in the treatment of panic disorder than CBT alone (Bakker *et al.* 1999; Oehrberg *et al.* 1995).

In general, patients with panic disorder should initially be treated with a low dosage of paroxetine (e.g., 10 mg/day), with gradual increases in dosage as clinically indicated. The data that led to FDA approval suggested that 40 mg/day was the minimum effective dosage for this condition;

however, clinical experience has shown that lower dosages may be sufficient for some patients and higher dosages may be required for other patients (Ballenger *et al.* 1998). The standard duration of treatment ranges from 6 to 12 months; however, rates of relapse for panic disorder appear to be greater than those for MDD, suggesting that panic disorder may require an indefinite course of treatment (Hirschfeld 1996).

Obsessive-Compulsive Disorder

Sertraline

Currently, the SSRIs fluvoxamine, fluoxetine, sertraline, and paroxetine are FDA approved for the treatment of OCD in adults. Several multicenter trials reported greater

benefit for sertraline versus placebo in the acute-and maintenance-phase treatment of OCD. One study did not show superiority of sertraline over placebo, perhaps because of the limited sample size (*n* = 19) or the treatment-resistant characteristics of the cohort (Jenike *et al.* 1990). Larger studies with diverse cohorts had differing results. By week 3 in a 12-week flexible-dose study in 167 patients (Kronig *et al.* 1999), sertraline (mean dosage 165 mg/day) had separated from placebo. At study endpoint, 41% of patients receiving sertraline (vs. 23% of those receiving placebo) had achieved a CGI-I score of 1 or 2.

In a fixed-dose multisite trial, Greist *et al.* (1995a) also found superior results with three different daily dosages (50, 100, or 200 mg) of sertraline compared with placebo over 1 year of treatment. Patients with OCD (*n* = 325) were randomly assigned to receive 12 weeks of double-blind treatment after a 1-week washout period. Responders (40% of sertraline-treated patients and 26% of placebo-treated patients) were offered enrollment in an additional 40 weeks of continuation treatment. Over the 52 weeks of the study, sertraline-treated patients demonstrated significantly greater improvement than did participants given placebo.

Some evidence suggests that higher daily dosages of sertraline may be helpful for patients whose symptoms do not respond to standard dosages. In one study, 66 patients with OCD that was unresponsive to sertraline therapy (200 mg/day) after 16 weeks of treatment were randomly assigned to continue on the same dosage for an additional 12 weeks or to increase their dosage (250-400 mg/day) (Ninan *et al.* 2006). At the end of the trial, patients taking higher dosages had greater improvement in Yale-Brown Obsessive Compulsive Scale scores, although rates of response were similar for the two groups.

Other studies supporting the utility of sertraline in OCD have included head-to-head comparisons with other antidepressants (e.g., vs. fluoxetine [Bergeron *et al.* 2002]; vs. clomipramine [Bisserbe *et al.* 1997]; vs. desipramine [Hoehn-Saric *et al.* 2000]). In a comparison of lower-dosage sertraline with cognitive-behavioral group therapy, both treatments were shown to be efficacious, although patients with OCD treated with group therapy had greater reductions in symptoms (Sousa *et al.* 2006). Continuation of CBT versus sertraline initiation in children and adolescents with OCD who had not responded to an initial trial of CBT resulted in similar efficacy (Skarphedinsson *et al.* 2015).

Sertraline is approved for use in children for the treatment of OCD. March *et al.* (1998) conducted a 12-week double-blind, placebo-controlled, parallel-group multicenter trial in 187 pediatric participants (107 children ages 6-12 years and 80 adolescents ages 13-17 years). They found that participants treated with sertraline (mean endpoint dosage 167 mg/day) showed significantly greater improvement in Yale-Brown Obsessive Compulsive Scale, National Institute of Mental Health Global Obsessive-Compulsive Scale, and CGI-I scores compared with those receiving placebo. There were few dropouts due to adverse events, and the authors concluded that sertraline is a safe, well-tolerated treatment in this age group (March *et al.* 1998). A subsequent study in children and adolescents treated with sertraline (50-200 mg/day) over 12 months reported that many who responded to acute treatment could achieve full or partial remission status with longer-term treatment (Wagner *et al.* 2003).

Paroxetine

Although two meta-analyses assessing the efficacy and tolerability of the TCA clomipramine and SSRIs in OCD seemed to favor clomipramine in terms of overall effectiveness (Greist *et al.* 1995b; Piccinelli *et al.* 1995), the only placebo-controlled multicenter study to compare clomipramine directly against an SSRI (paroxetine) revealed equal efficacy, with greater tolerability for paroxetine (Zohar *et al.* 1996).

Paroxetine also has demonstrated efficacy in pediatric OCD. In a randomized, double-blind, placebo-controlled multicenter trial (Geller *et al.* 2004), paroxetine was an effective and generally well-tolerated treatment for OCD in children and adolescents. Patients with comorbid MDD were excluded from this study, and only one incident of treatment-emergent suicidal behavior or ideation was reported.

In adults, paroxetine dosages of 60 mg/day or greater are usually required for optimal efficacy in OCD. Although patients usually respond to treatment within 3-4 weeks, clinical improvement may not be discernible until 10-12 weeks; therefore, a standard trial of up to 12 weeks should be conducted before an alternative medication is considered (Rasmussen *et al.* 1993).

Posttraumatic Stress Disorder

Sertraline

Among the SSRIs, sertraline and paroxetine have received FDA approval for the treatment of PTSD. Sertraline's efficacy in the treatment of PTSD is supported by two large acute-phase, double-blind, placebo-controlled multicenter studies (Brady *et al.* 2000; Davidson *et al.* 2001b), a long-term treatment study (Londborg *et al.* 2001), and a relapse prevention trial (Davidson *et al.* 2001a).

In the first acute-phase trial (Davidson *et al.* 2001b), 208 civilian patients were randomly assigned to receive either sertraline or placebo for 12 weeks. Observed rates of symptom reduction with active treatment were about 50% for reexperiencing/intrusion, just under 50% for avoidance/numbing, and 40% for arousal. The probability of response, defined as a CGI score of 1 or 2 and a minimal 30% decrease in Clinician-Administered PTSD Scale-Part 2 score, was 0.65 for sertraline-treated patients and 0.38 for placebo-treated patients at the 12-week endpoint. Approximately 40% of each group had comorbid MDD, with mean baseline 21-item Ham-D scores of around 21. Of interest, there were no significant differences among groups in depression symptom severity. The second acute-phase study (Brady *et al.* 2000) yielded similarly positive results.

In a pediatric sample with PTSD, 10 weeks of treatment with sertraline 50-200 mg/day appeared generally safe but did not produce outcomes superior to those with placebo (Robb *et al.* 2010).

Whereas the overall acute-phase efficacy of sertraline for PTSD was significant for women in the large controlled studies reviewed earlier (Brady *et al.* 2000; Davidson *et al.* 2001b), sertraline failed to differentiate from placebo in men. Some research suggests that treatment efficacy may vary by gender and by type of traumas experienced. Other research has shown no significant gender differences in sertraline's efficacy in patients with combat-related PTSD (Friedman *et al.* 2007). Reasons for the sex differences in efficacy findings are not clear, although one possible explanation is that women are more likely than men to experience sexual or physical trauma and childhood abuse. It is possible that the nature of the trauma itself (age at exposure, chronicity, or contextual factors) may alter the biology of the disorder and its responsiveness to medication (Stein *et al.* 2006).

Findings from a U.S. Department of Veterans Affairs medical center study failed to demonstrate that sertraline was superior to placebo for patients with predominantly combat-related PTSD (Friedman *et al.* 2007), but a subsequent trial in Iranian combat veterans (*n* = 70) did show a more robust efficacy for sertraline compared with placebo (Panahi *et al.* 2011).

Sertraline's long-term benefit for PTSD was demonstrated in a prospective study in which patients with PTSD who had completed 12 weeks of double-blind, placebo-controlled, acute-phase treatment with sertraline (Brady *et al.* 2000) were enrolled in a 24-week open-label continuation phase (Londborg *et al.* 2001). It was observed that about 20%-25% of the total improvement in PTSD symptoms occurred during the continuation phase (weeks 12-36). The greatest improvement over time was among patients who were originally considered "nonresponders" in the acute phase, leading the authors to conclude that as many as one-third of patients with PTSD may require longer treatment to achieve a clinically significant response. Sertraline's efficacy in sustaining improvement and preventing PTSD relapse was also examined in a 28-week double-blind continuation study ($n = 96$) (Davidson *et al.* 2001a). Sertraline was superior to placebo on the three primary outcome measures: full syndrome relapse (5.3% vs. 26.1%), relapse or discontinuation due to clinical deterioration (15.8% vs. 45.7%), and acute exacerbation (15.8% vs. 52.2%). The RR of relapse after discontinuing sertraline was 6.35.

A systematic review and meta-analysis concluded that trauma-focused psychotherapies should be considered first-line treatments for PTSD, while sertraline and venlafaxine appeared superior to other medications and should potentially be considered second-line treatments (Lee *et al.* 2016). However, a more recent study found no difference in efficacy for sertraline, prolonged exposure, or their combination (Rauch *et al.* 2019).

Paroxetine

Compared with placebo, paroxetine (20-40 mg/day) has been shown to produce significant improvements in the three symptom cluster groups of reexperiencing, avoiding/numbing, and hyperarousal and to reduce disability and depression (Marshall *et al.* 1998, 2001). Patients with PTSD and comorbid MDD respond just as favorably as do individuals without depression. Similar findings have been reported by other groups (Tucker *et al.* 2001, 2004), and paroxetine has also shown efficacy in combination with prolonged exposure therapy (Schneier *et al.* 2012) and in long-term treatment (Kim *et al.* 2008; Vermetten *et al.* 2003). A recent study found that paroxetine was less effective than prolonged exposure in achieving symptom remission, and the combination of paroxetine and prolonged exposure was not superior to prolonged exposure alone (Popiel *et al.* 2015).

Generalized Anxiety Disorder

Extended-release venlafaxine, escitalopram, duloxetine, and paroxetine have all been approved by the FDA for treatment of generalized anxiety disorder, whereas sertraline has not. The first published study supporting the use of paroxetine in generalized anxiety disorder compared it with both imipramine and 2'-chlordesmethyldiazepam, a benzodiazepine (Rocca *et al.* 1997). Not surprisingly, patients receiving the benzodiazepine showed the earliest improvement in symptoms; however, both paroxetine

and imipramine produced significant reductions in Hamilton Anxiety Scale total score, exceeding the reductions produced by the benzodiazepine by week 4 of the 8-week trial. Subsequent studies further confirmed the efficacy of paroxetine in the treatment of generalized anxiety disorder (Bielski *et al.* 2005; Pollack *et al.* 2001; Rickels *et al.* 2003).

Long-term treatment of generalized anxiety disorder with paroxetine may be necessary (Stocchi *et al.* 2003). Clinical experience and investigative research indicate that the usual effective paroxetine dosage for treating generalized anxiety disorder is 20 mg/day (GlaxoSmithKline 2019).

Sertraline has also shown some benefit in the treatment of generalized anxiety disorder. Two randomized generalized anxiety disorder trials showed that sertraline had superiority over placebo (Allgulander *et al.* 2004; Brawman-Mintzer *et al.* 2006), and another trial demonstrated that sertraline had efficacy similar to that of paroxetine (Ball *et al.* 2005). In a placebo-controlled trial (Rynn *et al.* 2001), sertraline was both effective and safe in children with generalized anxiety disorder.

Premenstrual Dysphoric Disorder

Sertraline

Fluoxetine, sertraline, and paroxetine are FDA approved for the treatment of premenstrual dysphoric disorder. The somatic features of premenstrual dysphoric disorder--bloating, weight gain, breast tenderness, poor concentration, and disturbed sleep and appetite--manifest in the luteal phase of ovulation and disappear with the onset of menstruation. These symptoms are cyclical, predictably appearing prior to each menses (Dimmock *et al.* 2000). The psychological symptoms of premenstrual dysphoric disorder are more severe and prominent and include irritability, dysphoria, tension, and mood lability. In one of the first multicenter trials to test the efficacy of an antidepressant agent for premenstrual dysphoric disorder, sertraline was compared with placebo (Yonkers *et al.* 1997). Either placebo or sertraline (at a flexible daily dosage of 50-150 mg) was given to each participant ($N =$ 243 women). After three menstrual cycles of treatment, total daily rating scores had decreased by 32% and 11% in the sertraline-and placebo-treated groups, respectively. Both emotional and physical symptom clusters improved by 32% with sertraline treatment, a reduction nearly threefold higher than that seen with placebo. At the endpoint, CGI-I scores of 1 or 2 were achieved by 62% and 34% of those assigned to sertraline and placebo, respectively.

In a second multicenter trial, it was shown that sertraline treatment could be commenced halfway through the menstrual cycle (i.e., at ovulation) and still be more effective than placebo (Halbreich *et al.* 2002). In this three-cycle, flexible-dosage study, 281 women were randomly assigned to receive sertraline 50-100 mg/day or placebo. The responder rates in this study, after three cycles of luteal-phase treatment, were 50% and 26% for sertraline and placebo, respectively. As with the daily treatment study, functional improvement paralleled symptomatic improvement. Only 8% of the women taking sertraline and 1% of the women receiving placebo discontinued the study because of side effects. The efficacy of this drug administration schedule for women with premenstrual dysphoric disorder has the potential to revolutionize treatment approaches, because many women with premenstrual dysphoric disorder prefer to avoid taking medication during nonsymptomatic periods.

A secondary analysis of data from three large federally sponsored trials (n = 447) indicated that women with premenstrual syndrome showed positive responses to sertraline, similar to outcomes observed for women with premenstrual dysphoric disorder (Freeman *et al.* 2011). Examination of symptom-based subtypes in that analysis revealed that predominantly psychological symptoms or mixed psychological and physical symptoms predicted better response to sertraline than did predominantly physical symptoms.

Paroxetine

Paroxetine has been shown to be significantly more effective than the tetracyclic maprotiline, a norepinephrine reuptake inhibitor, in reducing both psychological and somatic symptoms of premenstrual dysphoric disorder (Eriksson *et al.* 1995). Two small open trials reported positive findings with paroxetine treatment (Sundblad *et al.* 1997; Yonkers *et al.* 1996), and a double-blind, placebo-controlled study demonstrated that controlled-release paroxetine (25 mg/day) was both well tolerated and effective in the treatment of premenstrual dysphoric disorder (Cohen *et al.* 2004).

Premenstrual dysphoric disorder can be successfully managed with intermittent luteal-phase dosing, in which the medication is started 14 days before the estimated next menses and continued until the onset of menstruation (Steiner *et al.* 2005). It has been shown that paroxetine improves irritability within 14 hours of taking the first dose (Landen *et al.* 2009). Both luteal-and continuous-phase dosing of paroxetine (either the controlled-or immediate-release formulation) are superior to placebo in relieving the psychological symptoms of premenstrual dysphoric disorder, but not the somatic symptoms (food craving, breast tenderness) (Steiner *et al.* 2005, 2008). Somatic symptoms may be better addressed with continuous treatment (Landen *et al.* 2007; Wu *et al.* 2008); however, with intermittent dosing, patients experience fewer adverse effects (Steiner *et al.* 2008).

Menopausal Vasomotor Symptoms

In addition to its proven efficacy in premenstrual dysphoric disorder, paroxetine is efficacious in treating perimenopausal hot flashes (Simon *et al.* 2013; Soares *et al.* 2008; Stearns *et al.* 2003). In 2013, a new formulation--paroxetine mesylate 7.5-mg capsules, marketed as Brisdelle--became the first nonhormonal medication to receive FDA approval for this indication (Noven Therapeutics 2013). The mechanism of action may involve a paroxetine-induced increase in brain-derived neurotrophic factor (BDNF) plasma levels (Cubeddu *et al.* 2010). It should be noted that higher strengths of paroxetine mesylate have not been approved for treatment of menopausal vasomotor symptoms.

Earlier studies also showed paroxetine (20 mg/day) to be effective in the treatment of postmenopausal hot flashes in survivors of breast cancer who had experienced chemotherapy-induced ovarian failure (Stearns *et al.* 2000, 2005; Weitzner *et al.* 2002). However, it is important to consider the risks of paroxetine in women with estrogen receptor-positive breast cancer who are taking tamoxifen to decrease the risk of breast cancer relapse. Tamoxifen is a prodrug that requires CYP2D6 metabolism to create its more active metabolite, endoxifen; however, as a potent inhibitor of CYP2D6, paroxetine blocks the conversion of tamoxifen to endoxifen (Kelly *et al.* 2010). An increased risk of death from breast cancer has been observed for women taking tamoxifen and paroxetine (Kelly *et al.* 2010).

Sertraline has been proposed as an off-label treatment for women to alleviate hot flashes associated with menopause (Aedo *et al.* 2011; Gordon *et al.* 2006; Grady *et al.* 2007) and with tamoxifen treatment for breast cancer (Kimmick *et al.* 2006), as well as for men who have received androgen-deprivation therapy for advanced prostate cancer (Roth and Scher 1998). One study suggested that a positive response to sertraline for hot flashes is related to activity level, education, and menopausal status (Kerwin *et al.* 2007).

Sertraline was superior to placebo in a study that examined its potential for controlling hot flashes in women with or at high risk for breast cancer for whom hormone therapy was not recommended (Wu *et al.* 2009).

Side Effects and Toxicology

The popularity of SSRIs as a class in the treatment of psychiatric disorders is owed not to their superiority in efficacy over their predecessors but rather to their overall tolerability and safety. The most commonly reported side effects of sertraline in clinical trials are nausea, diarrhea or loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido (Pfizer 2021). The most commonly cited adverse experiences in patients treated with paroxetine are nausea, headache, somnolence, dry mouth, asthenia, sweating, constipation, dizziness, and tremor (Boyer and Blumhardt 1992).

Sexual Dysfunction

All SSRIs and serotonin-norepinephrine reuptake inhibitors have been associated with male and female sexual dysfunction. In a comparison study of 200 individuals, paroxetine treatment was associated with higher rates of anorgasmia in women and ejaculation difficulty or impotence in men compared with fluoxetine, fluvoxamine, and sertraline (Montejo-Gonzalez *et al.* 1997). In a large cross-sectional observational study (Clayton *et al.* 2002), paroxetine was associated with the highest rates of sexual dysfunction among the antidepressants evaluated (mirtazapine, venlafaxine, sertraline, citalopram, fluoxetine, nefazodone, and bupropion). More recently, paroxetine was reported to cause significantly worse sexual side effects than placebo in healthy control subjects (Jacobsen *et al.* 2019). In contrast, vortioxetine did not demonstrate similarly severe side effects (Jacobsen *et al.* 2019).

Sexual side effects emerge in a dose-dependent fashion and do not appear to diminish with prolonged administration; however, the effect is reversible, with most patients returning to normal functioning within 1 month of discontinuing the medication (Tanrikut *et al.* 2010). Strategies to lessen the impact of psychotropic medications on sexual function include reducing the dosage, changing to a different antidepressant with less sexual side-effect liability, and adding an agent (e.g., sildenafil, yohimbine, buspirone, cyproheptadine, amantadine, methylphenidate, bupropion) to reverse the sexual side effects (Rosen *et al.* 1999). A Cochrane Database review noted that although limited evidence is available, some trials have suggested that the addition of sildenafil or bupropion can reduce antidepressant-induced erectile dysfunction in men (Rudkin *et al.* 2004).

The sexual side effects of paroxetine have led to its use in the treatment of premature ejaculation. Paroxetine produces a greater delay in time to ejaculation compared with fluoxetine, fluvoxamine, sertraline, duloxetine, and mirtazapine (Safarinejad 2006; Waldinger *et al.* 1998, 2003), and a recent meta-analysis concluded that paroxetine is superior to placebo, fluoxetine, and escitalopram in the treatment of premature ejaculation (Zhang *et al.* 2019). Several studies have also reported sertraline's benefit in treating premature ejaculation (Arafa and Shamloul 2006; Biri *et al.* 1998).

Hemostasis

Sertraline, paroxetine, and other SSRIs have been associated with modification of hemostasis, related to blockade of platelet serotonin reuptake. Blockade may lead to serotonin depletion in platelets, which can result in inhibition of serotonin-induced platelet aggregation. This risk may be greater in patients with a preexisting platelet disorder (Halperin and Reber 2007). For example, in one retrospective series of cases describing patients who had received a ventricular assist device, use of an SSRI was associated with an increased risk of bleeding (Auschra *et al.* 2022).

Suicidality

In 2004, the FDA released a statement regarding a possible increased risk of suicidal thinking and suicide attempts in children and adolescents age 18 or younger who are treated with antidepressants, including sertraline and paroxetine, for MDD (Newman 2004). The statement was based on data from three well-controlled unpublished studies, each showing no benefit for paroxetine over placebo in the treatment of pediatric depression. The data also revealed an increased rate of suicidal ideation and suicide attempts with paroxetine treatment versus placebo (3.4% vs. 1.2%). There are no specific data indicating increased rates of suicide in children treated with sertraline.

In late 2006, an FDA advisory committee extended the black box warning to cover young adults up to their mid-20s (Friedman and Leon 2007). The committee reported that 1) in patients ages 18-24 years, antidepressant use was associated with four cases of suicidal ideation per 1,000 patients treated; 2) there was no evidence of increased risk in adults older than 24 years; and 3) antidepressant treatment was unequivocally protective against suicidality in patients ages 65 years and older.

Clinicians should inform their patients about the possible risks and should monitor patients with depression closely when they prescribe sertraline, paroxetine, or any other antidepressant, particularly during the early phase of treatment. The FDA advisory committee has made it clear that the black box warning should not dissuade physicians from prescribing antidepressants to patients in need (Friedman and Leon 2007).

Hyponatremia

Sertraline, paroxetine, and other SSRIs have been associated with cases of hyponatremia as well as with the syndrome of inappropriate antidiuretic hormone (SIADH) secretion (see Bouman *et al.* 1997; Bradley *et al.* 1996; Catalano *et al.* 1996; Goldstein *et al.* 1996; Kessler and Samuels 1996). In a review of the literature, Bradley *et al.* (1996) noted that patients experiencing SIADH were older than age 70 years on average, suggesting that elderly individuals may be more vulnerable to age-related changes in water balance, which may make them more susceptible to developing SIADH with an SSRI.

Extrapyramidal Side Effects

Extrapyramidal side effects, including dyskinesias, dystonias, and akathisia, have been observed with the use of SSRIs, including sertraline and paroxetine, although they are infrequent (Altshuler and Szuba 1994; Lambert *et al.* 1998; Madhusoodanan and Brenner 1997; Opler 1994; Revet *et al.* 2020). Hamilton and Opler (1992) suggested that the underlying mechanism of SSRI-induced akathisia is serotonergic inhibition of the nigrostriatal dopamine pathway, which can be associated with parkinsonism (Leo *et al.* 1995; Pina Latorre *et al.* 2001). Madhusoodanan and Brenner (1997), in a case report of choreiform dyskinesia and extrapyramidal side effects associated with sertraline therapy, proposed that serotonin-driven antagonism of dopaminergic transmission in the nigrostriatal pathway, as well as in the ventral tegmental area, might be responsible.

Discontinuation Syndrome

With abrupt discontinuation or treatment interruption, patients may develop what has become known as SSRI discontinuation syndrome. Symptoms (e.g., dizziness, paresthesias, agitation, anxiety, nausea, and sweating) occur as early as the second day after a missed dose and may persist for several days. A comparison of SSRI postmarketing safety data reported that withdrawal-related events occurred more frequently in patients treated with paroxetine than in individuals treated with sertraline, fluvoxamine, or fluoxetine and these events had a mean duration of 10.2 days (Price *et al.* 1996); similar results were reported by other groups (Michelson *et al.* 2000; Montgomery *et al.* 2004; Rosenbaum *et al.* 1998). Studies examining the effect of shorter SSRI treatment interruptions (3-5 days)--similar to what a patient would experience if they missed just a few medication doses--found that whereas paroxetine-treated patients develop significant discontinuation-emergent effects, fluoxetine-treated patients do not, a disparity likely due to differences in the half-lives of these medications (Judge *et al.* 2002; Michelson *et al.* 2000). In a systematic 28-week study in patients with panic disorder (Rapaport *et al.* 2001), abrupt discontinuation of sertraline was primarily associated only with insomnia (15.7% of patients randomly assigned to placebo vs. 4.3% continuing on sertraline) and dizziness (16.4% of patients switched to placebo vs. 4.3% continuing on sertraline). There was no statistically significant increase in headache or general malaise in patients randomly assigned to switch to placebo.

Use During Pregnancy and Lactation

The safety of sertraline, paroxetine, and other SSRIs during pregnancy is discussed in Chapter 63 ("Psychopharmacology During Pregnancy and Lactation"). A large-scale study in Quebec reported that exposure to sertraline during the first trimester was associated with an increased risk of cardiac (atrial or ventricular) effects and craniosynostosis (Berard *et al.* 2015). A recent meta-analysis of cohort studies also found that sertraline was associated with septal defects, atrial septal defects, and respiratory system defects (Gao *et al.* 2018).

Paroxetine was the only SSRI to be allocated to FDA Pregnancy Category D ("There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks") (U.S. Food And Drug Administration (2021), although the FDA pregnancy letter categories were removed with adoption of the pregnancy and lactation labeling rule (PLLRL) in 2015 (U.S. Food And Drug Administration (2014). Spontaneous abortion has been linked both to depression and to antidepressant use; the risk may be even greater for women who are treated with paroxetine or venlafaxine (Nakhai-Pour *et al.* 2010). Compared with other SSRIs, however, paroxetine has lower transmission across the placenta, and cord blood concentrations do not correlate with maternal dosing (Hendrick *et al.* 2003b). Maternal CYP2D6 polymorphisms appear to affect the pharmacokinetics of paroxetine. Women characterized as extensive metabolizers show decreases in paroxetine plasma levels over the course of pregnancy, whereas women characterized as intermediate or poor metabolizers show increased paroxetine levels (Ververs *et al.* 2009). It is possible that this effect may translate to a greater risk of fetal teratogenicity for women who are poor or intermediate metabolizers (Ververs *et al.* 2009).

Teratogenicity is a major concern when prescribing medications to women of childbearing age. The results of an unpublished study by GlaxoSmithKline (Paxil) led the FDA to warn that paroxetine may increase the risk of major congenital malformations (Williams and Wooltorton 2005). Several organ systems, including the CNS and gastrointestinal genitourinary systems, were affected; the most common cardiovascular anomalies were ventricular septal defects. A meta-analysis, also completed by GlaxoSmithKline, found a prevalence OR of 1.46 for combined cardiac defects with exposure to paroxetine in the first trimester. Considering a background prevalence of cardiac defects in the unexposed population of 1%, this would represent a 50% increase for the paroxetine-exposed population (Wurst *et al.* 2010).

In a cohort study comparing rates of major congenital malformations in infants born to women treated with paroxetine, fluvoxamine, or sertraline during pregnancy, researchers found no significant differences among the medication groups compared with the control group (Kulin *et al.* 1998). In another study comparing birth outcomes after prenatal exposure to paroxetine, fluoxetine, or sertraline, rates of neonatal complications and congenital malformations in antidepressant-exposed infants were lower (1.4%) than rates in the general population, with no significant differences among medications (Hendrick *et al.* 2003a). Whereas one prospective controlled observational study reported no increased risk of cardiac defects with paroxetine exposure (Diav-Citrin *et al.* 2008), a case-control study of data from a population-based registry of birth defects in the Netherlands showed an increased risk of atrial septal defects with first-trimester paroxetine exposure (adjusted OR, 5.7; 95% CI, 1.4-23.7) (Bakker *et al.* 2010). A meta-analysis of 23 studies concluded that paroxetine exposure during the first trimester was associated with a significantly increased risk of major congenital malformations, particularly major cardiac malformations (Berard *et al.* 2016). Another meta-analysis also found that paroxetine was associated with major congenital anomalies and congenital heart defects (Gao *et al.* 2018). It is important to

note that studies of teratogenicity are frequently complicated by the effects of depression itself or of polypharmacy (e.g., concurrent use of benzodiazepines) (Yonkers *et al.* 2009). Nevertheless, on the basis of the risk of malformations, the American College of Obstetricians and Gynecologists has recommended that paroxetine be avoided, if possible, in pregnant women or women planning pregnancy (ACOG Committee on Practice Bulletins--Obstetrics 2008).

Clinical studies of paroxetine in the setting of pregnancy suggest that gestational exposure might have transient negative effects on the newborn infant, particularly if the mother is treated during the third trimester. Infants with third-trimester paroxetine exposure show significantly increased distress compared with infants not so exposed (Costei *et al.* 2002). Symptoms in neonates exposed to SSRIs in utero include tremor, hypertonicity, irritability, weak or absent cry, seizures, and poor feeding; these symptoms typically resolve within 2 weeks (Knoppert *et al.* 2006; Yonkers *et al.* 2009). Debate continues among neonatologists as to whether this neonatal distress represents a manifestation of serotonin excess or serotonin withdrawal (Laine *et al.* 2004; Stiskal 2005, 2006).

If a woman opts to continue antidepressant treatment during pregnancy, the clinician is advised to monitor for relapse, given that higher dosages are often needed, especially in the early third trimester, to achieve or maintain disease remission (Hostetter *et al.* 2000).

A major review of SSRIs in breastfeeding concluded that sertraline and paroxetine are the preferred agents (in regard to the infant's health) for nursing women who require antidepressant treatment (Orsolini and Bellantuono 2015).

Drug-Drug Interactions

Combinations of medications that enhance serotonergic activity may result in serotonin toxicity (serotonin syndrome), manifesting as agitation, myoclonus, hyperreflexia, diarrhea, diaphoresis, delirium, fever, and possibly death (Weiner *et al.* 1997). Concomitant use of MAOIs with any of the SSRIs is absolutely contraindicated, and a washout period of 14 days is recommended when switching from one agent to another (Gunasekara *et al.* 1998; Weiner *et al.* 1997). Evidence of serotonin toxicity has been documented in case reports describing coadministration of paroxetine with moclobemide (Hawley *et al.* 1996), nefazodone (John *et al.* 1997), dextromethorphan (Skop *et al.* 1994), imipramine (Weiner *et al.* 1997), trazodone (Reeves and Bullen 1995), or other agents. The combination of SSRIs and sumatriptan, a serotonin$_{1D}$ receptor agonist used in the treatment of migraine, was previously discouraged because of the theoretical risk of precipitation of serotonin toxicity; however, a series of six cases, two involving sertraline and one involving paroxetine, of concurrent sumatriptan and SSRI administration demonstrated no such adverse events (Leung and Ong 1995).

Sertraline

Sertraline has a number of potential drug-drug interactions. Because the drug is tightly bound to plasma proteins, caution should be taken when sertraline is used in combination with pharmaceuticals possessing similar characteristics (e.g., warfarin),

and prothrombin time should be monitored when sertraline and warfarin are used concurrently (Pfizer 2021).

The degree of sertraline's inhibition of the CYP system, most significantly CYP2D6, is relatively minor compared with that of other SSRIs such as fluoxetine and paroxetine (Preskorn *et al.* 2007), although mouse data have shown a mild pharmacokinetic drug-drug interaction between bupropion and sertraline that leads to a small elevation in bupropion metabolism (Molnari *et al.* 2012). Because TCAs are substrates of CYP2D6, drug levels and dosages must be closely monitored when TCAs are used in combination with sertraline.

Sertraline, in common with its fellow SSRIs citalopram and escitalopram, is also metabolized by the CYP2C19 isoenzyme, which is inhibited by proton pump inhibitors. In a study examining the effect of proton pump inhibitors on serum concentrations of SSRIs, coadministration of esomeprazole led to significant elevations (+ 38.5%; $P = 0.0014$) in sertraline blood levels but caused an almost twofold increase (+ 81.8%; $P < 0.001$) in escitalopram blood levels (Gjestad *et al.* 2015).

Paroxetine

Paroxetine is dependent primarily on the CYP2D6 hepatic enzyme for conversion into its inactive metabolites (Hiemke and Hartter 2000). Paroxetine is not only a substrate of this system but also an inhibitor; therefore, other drugs that are metabolized by CYP2D6 are potentially subject to decreased clearance and subsequent increased plasma concentrations (Sindrup *et al.* 1992b). Concern is greatest for potential drug-drug interactions when the medication in question has a low therapeutic index.

Medications that are CYP2D6 dependent include many antipsychotics, TCAs, class IC antiarrhythmics, b-adrenergic agents, trazodone, and dextromethorphan (Nemeroff *et al.* 1996). Most reports of interactions between these medications and paroxetine are published as case reports (Lane 1996). As discussed earlier (see section "Menopausal Vasomotor Symptoms"), the breast cancer medication tamoxifen is converted to its active metabolite by CYP2D6, and there is evidence that paroxetine decreases the efficacy of tamoxifen and increases mortality in women with breast cancer who are taking tamoxifen (Kelly *et al.* 2010).

Paroxetine does not appear to potentiate the sedative effects of haloperidol (Cooper *et al.* 1989); however, dystonia has been reported with the combination (Budman *et al.* 1995). In one prospective study, clozapine serum levels increased by an average of 40% when clozapine was coadministered with SSRIs, including paroxetine at a mean dosage of 31.2 mg/day (Centorrino *et al.* 1996). In another study that used a lower dosage of paroxetine (20 mg/day), no significant increase in clozapine concentrations was noted (Wetzel *et al.* 1998). There is insufficient evidence to draw conclusions about the clinical significance of interactions between paroxetine and other second-generation antipsychotics (Spina and de Leon 2014). Case reports have described possible exaggeration of extrapyramidal side effects when paroxetine was coadministered with perphenazine (Ozdemir *et al.* 1997), molindone (Malek-Ahmadi and Allen 1995), or pimozide (Horrigan and Barnhill 1994).

Paroxetine was found to increase total exposure (i.e., area under the curve of plasma concentrations) to the b-adrenergic receptor antagonist nebivolol by a factor of 6.1 (Briciu *et al.* 2014). Paroxetine also increased plasma concentrations of the b-adrenergic

receptor antagonist timolol (administered as eye drops) to a level that could cause systemic adverse events in at-risk patients (Maenpaa *et al.* 2014).

Paroxetine is highly protein bound and has the potential to increase free drug levels of other medications that are bound to plasma proteins, such as warfarin, lithium, and digoxin, although this effect is rarely clinically meaningful (Bannister *et al.* 1989; Haenen *et al.* 1995; Preskorn 1993).

In prospective studies involving valproate, carbamazepine, or phenytoin, coadministration with paroxetine did not cause significant changes in plasma levels of these drugs (Andersen *et al.* 1991; Kaye *et al.* 1989). By contrast, both phenytoin and carbamazepine have been shown to decrease plasma paroxetine concentrations (Hiemke and Hartter 2000; Kaye *et al.* 1989). Valproate may increase plasma paroxetine concentrations (Andersen *et al.* 1991). Cimetidine, which is a potent inhibitor of the CYP2D6 isoenzyme, has been shown to result in a 50% elevation of paroxetine concentrations (Bannister *et al.* 1989). The clinical significance of these variations in paroxetine concentrations is minor because of its wide interindividual pharmacokinetic variability, high therapeutic index, and lack of a concentration-efficacy relationship (Gunasekara *et al.* 1998).

Paroxetine does not potentiate the psychomotor effects of amobarbital, oxazepam, diazepam, or alcohol (Bannister *et al.* 1989; Cooper *et al.* 1989).

Conclusion

Controlled clinical trials support sertraline and paroxetine's efficacy in the treatment of a variety of psychiatric conditions, including depressive and anxiety disorders. The safety profiles of sertraline and paroxetine are superior to those of older antidepressant agents, thus increasing the potential target population of patients for whom treatment can be beneficial.

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CHAPTER 14

Citalopram and Escitalopram

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Citalopram (Celexa) and its pharmacologically active enantiomer, escitalopram (Lexapro), are among the most selective serotonin reuptake inhibitors available. Both drugs are widely prescribed and have been shown in large-scale controlled trials to be effective in the treatment of depression; escitalopram has also been shown to be effective in the treatment of anxiety disorders. Generic formulations of both drugs are now available. Both drugs are well tolerated by patients and show a low potential for pharmacokinetic drug-drug interactions, although higher-dosage citalopram treatment is associated with a clinically significant QT prolongation. Citalopram and escitalopram have similar effectiveness in the treatment of depression, although some studies suggest a modest superiority of escitalopram over citalopram on some measures of efficacy, including a possibly faster onset of therapeutic effect for escitalopram. Antagonism of the effects of escitalopram by *(R)*-citalopram has been invoked to explain the purported therapeutic differences between the two drugs. In addition, the affinity of citalopram for histamine receptors appears to reside in the *(R)*-enantiomer, suggesting that escitalopram has a decreased potential for antihistaminergic side effects. Finally, in terms of cardiac safety, citalopram has a greater potential to prolong the electrocardiographic QT interval and produce potentially serious arrhythmias.

History and Discovery

The pharmacology of citalopram was first described in 1977 (Christensen *et al.* 1977; Hyttel 1977). Citalopram was shown to be a very potent inhibitor of serotonin reuptake in both in vitro and in vivo models, with an inhibition constant (K_i) of approximately 1.5 nM (Hyttel 1977, 1978). It was subsequently discovered that all of the inhibitory activity of citalopram on serotonin reuptake resides in the *(S)*-(+)-enantiomer (escitalopram), with a K_i of approximately 1 nM (Hyttel *et al.* 1992; Owens *et al.* 2001; Sanchez *et al.* 2014). Originally introduced in Denmark in 1989, citalopram was approved by the FDA for the treatment of depression in July 1998. Citalopram is licensed in the United Kingdom and Europe for both depression and panic disorder; however, it is not FDA approved for the latter indication. Escitalopram received FDA approval for the treatment of major depressive disorder (MDD) in August 2002 and for the treatment of generalized anxiety disorder in December 2003. In addition, escitalopram received FDA approval in March 2009 for the treatment of MDD in adolescents ages 12-17 years.

Structure-Activity Relations

Citalopram has a single chiral center (Figure 14-1). A chiral center is an atom surrounded by an asymmetrical arrangement of atoms such that the three-dimensional configuration is not superimposable on its mirror image. At this chiral center, there are two possible stereoisomers. Often, drugs are produced as a mixture of both stereoisomers, referred to as the *racemate*. However, in some instances, different stereoisomers may have varying pharmacodynamics, pharmacokinetics, or toxicity, such that one form may be superior (Agranat *et al.* 2002). Citalopram was originally developed and marketed as the racemate, but subsequently the isolated stereoisomer of citalopram, escitalopram (Figure 14-2), was developed for the treatment of depression and other psychiatric disorders. Preclinical studies indicate that inhibition of serotonin transporter activity resides predominantly in the *(S)*-enantiomer (Hyttel *et al.* 1992), with escitalopram being over 30 times more potent than *(R)*-citalopram at inhibiting serotonin transport (K_i = 1.1 vs. 36 nM) (Owens *et al.* 2001).

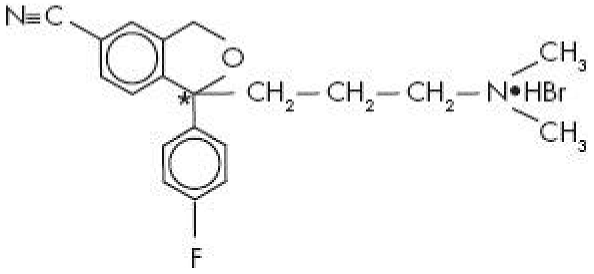

FIGURE 14-1. Chemical structure of citalopram hydrobromide.

*Indicates chiral center.

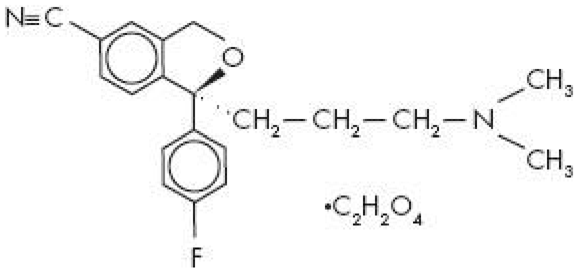

FIGURE 14-2. Chemical structure of escitalopram oxalate.

A possible explanation for the postulated modest superiority of escitalopram over citalopram on some measures of antidepressant efficacy is provided by evidence showing that the *(R)*-enantiomer of citalopram may interfere with the activity of the *(S)*-enantiomer, as demonstrated in several behavioral and physiological assays (for a review, see Sanchez 2006). In rat brain microdialysis studies, the administration of escitalopram with escalating levels of *(R)*-citalopram reduced serotonin reuptake blockade in a dose-dependent manner (Mork *et al.* 2003). Notably, *(R)*-citalopram and escitalopram in racemic citalopram have different clearance rates, resulting in an *(R)*-citalopram/escitalopram ratio of 2:1 (Brosen and Naranjo 2001). This antagonism has been hypothesized to result from a kinetic interaction at the serotonin transporter (Storustovu *et al.* 2004). Specifically, escitalopram is an allosteric modulator of the serotonin transporter; *(R)*-citalopram binds allosterically to the transporter, resulting in a conformation change that reduces the binding time of escitalopram (Sanchez 2006). Although there are effects in preclinical models, differences clinically are modest.

Pharmacological Profile

Citalopram

Of the selective serotonin reuptake inhibitors (SSRIs) approved to date, citalopram is one of the most selective, with a 524-fold lower potency for inhibiting the human norepinephrine transporter and a greater than 10,000-fold lower potency for inhibiting the human dopamine transporter (Owens *et al.* 2001). In addition, citalopram has low affinity for a wide variety of neurotransmitter receptors (for a review, see Hyttel *et al.* 1995). Citalopram has been reported to have submicromolar affinity for the histamine$_1$ receptor (K_i = 283 nM) (Hyttel 1994; Richelson and Nelson 1984), but this appears to be true only for the *(R)*-enantiomer (Owens *et al.* 2001). Citalopram does not show significant inhibition of monoamine oxidase (Hyttel 1977). Behavioral studies in rats and mice have shown citalopram to be a potent and selective inhibitor of serotonin reuptake (Christensen *et al.* 1977; Hyttel 1994). In contrast, citalopram has no in vivo effects on dopamine or norepinephrine reuptake (Hyttel 1994). Citalopram is active in various behavioral models related to antidepressant activity (Martin *et al.* 1990; Sanchez and Meier 1997) and anxiolytic activity (Inoue 1993; Sanchez 1995).

Escitalopram

Escitalopram is also a highly potent inhibitor of serotonin reuptake, with a K_i for binding to the human serotonin transporter of 1.1 nM, compared with 1.9 nM for citalopram and 36 nM for *(R)*-citalopram (Owens *et al.* 2001). Escitalopram is the most selective SSRI approved for clinical use, with a 2,600-fold lower potency for inhibiting the human norepinephrine transporter and a greater than 45,000-fold lower potency for inhibiting the human dopamine transporter. Escitalopram has no appreciable binding affinity for a large number of other neurotransmitter receptors (Owens *et al.* 2001; Sanchez *et al.* 2003). Escitalopram shows potent activity in various in vivo paradigms, including a model of serotonin reuptake inhibition and behavioral models of antidepressant, antiaggressive, and anxiolytic activity (for a review, see Sanchez *et al.* 2003). In these in vivo paradigms, escitalopram's potency ranges from being similar to that of citalopram to being approximately twofold greater than that of citalopram. In contrast, in the majority of these paradigms, *(R)*-citalopram is severalfold less potent than either escitalopram or citalopram.

Pharmacokinetics and Disposition

Citalopram

Citalopram is well absorbed after oral administration, with an absolute bioavailability of 80% for citalopram tablets (Joffe *et al.* 1998). The peak plasma concentration is normally observed 2-4 hours after an oral dose (Kragh-Sorensen *et al.* 1981). The bioavailability of citalopram is not affected by food (Baumann 1992), and it is subject to very little first-pass metabolism (Kragh-Sorensen *et al.* 1981). The apparent volume of distribution is 12-16 L/kg (Fredricson Overo 1982; Kragh-Sorensen *et al.* 1981), which indicates that the drug distributes widely. There is a linear relationship between steady-state plasma concentration and dose (Bjerkenstedt *et al.* 1985), and plasma protein binding is about 80% (Baumann 1992). Systemic clearance of citalopram is 0.3-0.4 L/minute (Baumann 1992), and renal clearance of citalopram is approximately 0.05-0.08 L/minute (Sindrup *et al.* 1993).

Racemic citalopram undergoes *N*-demethylation by the hepatic cytochrome P450 (CYP) system to the major metabolite monodesmethylcitalopram (DCT). Enzymes CYP2C19, CYP3A4, and CYP2D6 all contribute approximately equally to the formation of DCT (Kobayashi *et al.* 1997; Rochat *et al.* 1997; von Moltke *et al.* 1999). DCT also undergoes *N*-demethylation to the minor metabolite didesmethylcitalopram by the actions of CYP2D6 (Sindrup *et al.* 1993; von

Moltke *et al.* 2001). Clinical studies indicate that the half-lives for citalopram, DCT, and didesmethylcitalopram are approximately 36, 50, and 100 hours, respectively (Dalgaard and Larsen 1999; Fredricson Overo 1982; Kragh-Sorensen *et al.* 1981). Citalopram is metabolized by human cytochromes that display genetic polymorphisms, and metabolism of citalopram and DCT is impaired in patients who show poor metabolism via the CYP2C19 and CYP2D6 pathways (Baumann *et al.* 1996; Sindrup *et al.* 1993; Yu *et al.* 2003).

Escitalopram

The clinical pharmacokinetics of escitalopram were reviewed by Rao (2007). The clearance of *(S)*- and *(R)*-citalopram differs, such that the levels of the *(R)*-enantiomer are higher than the *(S)*-enantiomer when racemic citalopram is given. Therefore, doses of citalopram and escitalopram are not 2:1 (Brosen and Naranjo 2001)--that is, citalopram 20 mg has lower amounts of escitalopram than when escitalopram 10 mg is administered. This variation may account for some of the modest differences in clinical outcomes mentioned earlier (Auquier *et al.* 2003). Escitalopram has 56% protein binding, making it safer to administer with other drugs that are highly protein bound than citalopram (Rao 2007).

Mechanism of Action

The majority of studies on mechanism of action have focused on citalopram, with a relatively limited number of studies using escitalopram. Because the antidepressant activity of citalopram results from escitalopram, the majority of the conclusions from these studies pertain to both medications.

Citalopram is a potent and selective inhibitor of serotonin reuptake and acts by binding directly to the serotonin transporter. Citalopram more selectively inhibits radioligand binding to the serotonin transporter (K_i = 0.75 nM) than to the norepinephrine transporter (K_i = 3,042 nM) in rat cortical membranes. A similar selectivity was found for inhibition of the binding of the same radioligands to the cloned human serotonin and norepinephrine transporters expressed in transfected cells and for inhibition of [3H]-serotonin (K_i = 8.9 nM) and [3H]-norepinephrine (K_i = 30,285 nM) reuptake into these transfected cells (Owens *et al.* 1997).

Several studies have described how repeated dosing alters the effects of citalopram on serotonergic neuronal function. As with other SSRIs, the ability of citalopram to inhibit the firing of serotonin neurons in the dorsal raphe nucleus is greatly reduced after 14 days of repeated administration (Chaput *et al.* 1986). This change is associated with an increase in the ability of citalopram to elevate the extracellular levels of serotonin in the cortex (Invernizzi *et al.* 1994). These two effects appear to result from a desensitization of serotonin_{1A} autoreceptors (Chaput *et al.* 1986; Cremers *et al.* 2000; Invernizzi *et al.* 1994). This adaptive change of serotonin_{1A} receptors after repeated administration of citalopram, or other SSRIs, has been postulated to underlie the slow onset of antidepressant efficacy that is observed clinically (Blier and de Montigny 1994).

Evidence suggests that a variety of antidepressants, including those that block monoamine reuptake or metabolism, produce their therapeutic response in part by overcoming depression-associated decreases in neurogenesis and synaptogenesis, which is likely to be the result of effects on brain-derived neurotrophic factor (BDNF) expression, and possibly other neurotrophins such as vascular endothelial growth factor (Deyama *et al.* 2019). Citalopram, like many other antidepressants, has been shown to increase the levels of BDNF messenger RNA (mRNA) in various subregions of the rat ventral hippocampus (Russo-Neustadt *et al.* 2004) and to induce signaling through the BDNF receptor tyrosine kinase receptor TrkB (Rantamaki *et al.* 2007). In addition, citalopram was shown to enhance BDNF expression in neural crest-derived PC12 cells and enhance cell survival (Tan *et al.* 2010). Both citalopram and escitalopram were shown to increase peripheral blood BDNF in human patients with MDD (Zhou *et al.* 2017), an effect that has been shown with many antidepressants. Like other antidepressants, BDNF synthesis, release, and downstream actions on neurogenesis and synaptogenesis appear to be important targets of citalopram and escitalopram (Duman and Duman 2015).

A number of studies have implicated the serotonin$_{2A}$ (5-HT$_{2A}$) receptor in a variety of neuropsychiatric disorders (Norton and Owen 2005), and there is evidence implicating this receptor in the mechanism of action of antidepressants, including citalopram (Chen and Lawrence 2003; Peremans *et al.* 2005). In addition, a large-scale clinical study involving 1,953 patients who participated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial identified a significant association between a polymorphism contained in the second intron of the gene for the 5-HT$_{2A}$ receptor (rs7997012) and treatment response to citalopram, although the absolute effect was small (McMahon *et al.* 2006).

Several cellular and in vivo animal model studies have shown that antidepressants can increase glucocorticoid receptor (GR) translocation, induce GR downregulation, and decrease GR agonist-mediated effects (Anacker *et al.* 2011; Carvalho and Pariante 2008), and there is evidence suggesting that similar effects occur in vivo in humans. In a double-blind, placebo-controlled, crossover study in healthy men, treatment for 4 days with citalopram 20 mg/day was associated with a diminished ability of cortisol to increase electroencephalogram alpha power and to impair working memory (Pariante *et al.* 2012). These results suggest that GR activation by antidepressants does occur in the human brain.

Corticotropin-releasing factor (CRF) mediates many of the effects of psychological stress and is postulated to play a role in the pathophysiology of depression and anxiety disorders (Arborelius *et al.* 1999). In rats, lentiviral-mediated chronic elevation of amygdala CRF reproduces many of the behavioral and endocrine consequences of chronic stress that are consistent with a depressive or anxious phenotype (Flandreau *et al.* 2012). Interestingly, chronic escitalopram treatment of these CRF-overexpressing rats for 4 weeks reversed some but not all of the CRF-induced anxiety-like and depressive-like behavioral alterations (Flandreau *et al.* 2013).

Indications and Efficacy

Depression

Citalopram

The efficacy of citalopram (dosage range, 20-80 mg/day) in the treatment of depression has been shown in at least 11 placebo-controlled clinical trials (for a review, see Keller 2000). In addition, meta-analyses of multiple placebo-controlled studies reported similar findings (Bech and Cialdella 1992; Montgomery *et al.* 1994). In the United States, three large multicenter registration clinical trials demonstrated citalopram's efficacy in the treatment of MDD (Feighner and Overo 1999; Mendels *et al.* 1999; Stahl 2000). Primary care patients in the United Kingdom were given citalopram 20 mg/day (*n* = 274) or the norepinephrine reuptake inhibitor reboxetine 4 mg tid (*n* = 272); both medications were equally effective in the treatment of severe depression (defined as a Beck Depression Inventory score of 15 or greater) (Wiles *et al.* 2012). One large-scale meta-analysis reported that the efficacy of both citalopram and escitalopram was equal to that of other drugs, but both were more tolerable than many other drugs (Cipriani *et al.* 2018). As noted earlier, the analysis reported that escitalopram may be more effective than citalopram. Overall, there is ample evidence of acceptable efficacy and tolerability of citalopram.

Sequenced Treatment Alternatives to Relieve Depression trial.

The effectiveness of citalopram was also demonstrated in a study designed to simulate real-world conditions for the treatment of depression. STAR*D was a large-scale multicenter study that enrolled 4,041 patients with nonpsychotic MDD in a test of various antidepressant therapies (Rush *et al.* 2004). The mean dosage of citalopram at study exit was 41.8 mg/day. Remission rates were 28% when remission was defined as a score of 7 or less on the 17-item version of the Hamilton Rating Scale for Depression (Ham-D) and 33% when defined as a score of 5 or less on the 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) (Trivedi *et al.* 2006). The response rate was 47% when response was defined as a50% or greater reduction in QIDS-SR score (Trivedi *et al.*

2006). These response and remission rates are comparable to those found in 8-week controlled clinical trials examining the efficacy of acute antidepressant treatment.

Long-term treatment with citalopram. Two placebo-controlled studies indicated that citalopram may be effective in continuation therapy to prevent depression relapse (Montgomery *et al.* 1993; Robert and Montgomery 1995). Both studies showed that for patients with an acute therapeutic response to citalopram, continuation of citalopram therapy at the same dosage (20, 40, or 60 mg/day) for an additional 24 weeks significantly decreased the relapse rate compared with placebo (Montgomery *et al.* 1993; Robert and Montgomery 1995). Two additional studies suggested that citalopram may be beneficial for patients with a history of recurrent depression. Long-term (at least 48 weeks) administration of citalopram at the same fixed dosage at which patients initially showed therapeutic response (20-60 mg/day) can significantly increase the time before depression recurs in adult patients (ages 18-64 years) and in elderly patients (age 65 years and older) (Hochstrasser *et al.* 2001; Klysner *et al.* 2002).

Escitalopram

A number of placebo-controlled clinical trials and retrospective analyses have demonstrated the efficacy of escitalopram (dosage range, 10-20 mg/day) in the treatment of MDD (Burke *et al.* 2002; Lepola *et al.* 2003; Montgomery *et al.* 2001; Wade *et al.* 2002). In addition, a large number of retrospective pooled analyses have compared escitalopram with other SSRIs (Einarson 2004; Kennedy *et al.* 2006; Llorca *et al.* 2005). In general, escitalopram was at least as effective as other widely used antidepressants; in some clinical trials, escitalopram was suggested to be superior to other antidepressants based on modestly greater score changes on various depression rating scales, especially for patients with severe depression. In addition, escitalopram has been suggested in a few clinical trials to possibly have a faster onset of therapeutic effect (based on changes in depression rating scale scores), occurring as early as week 1, as indicated by a small but significant difference in depression severity ratings, as contrasted with comparator drugs (Auquier *et al.* 2003). It is unlikely that the small differences early in treatment translate into improved early results in clinical practice.

Long-term treatment with escitalopram. In a 36-week placebo-controlled clinical trial, participants given escitalopram 10-20 mg/day (*n* = 181) were less likely to experience relapse after resolution of a depressive episode than were those given placebo (*n* = 93) (Rapaport *et al.* 2004). In addition, the effectiveness of long-term escitalopram therapy in the prevention of depression recurrence was also demonstrated in a group of patients diagnosed with recurrent MDD (Kornstein *et al.* 2006). Patients given escitalopram 10 or 20 mg/day (*n* = 73) in this 52-week study had a significantly prolonged time to recurrence compared with those given placebo (*n* = 66).

International Study to Predict Optimized Treatment in Depression.

Treatment of depression may be significantly improved with the discovery of biomarkers that can identify which patients will respond best to which treatments. For example, depression is associated with impairments in a wide range of cognitive and emotional functioning (Snyder 2013). The International Study to Predict Optimized Treatment in Depression (iSPOT-D) trial was intended to determine whether laboratory measures of impaired functioning can be used to predict antidepressant treatment outcomes. In one report, medication-free outpatients with nonpsychotic MDD (*n* = 665 completers) were assessed before treatment with 13 computerized tests of cognitive and emotional functioning, and their performance was compared with that of healthy control subjects (*n* = 336). Patients were then randomly assigned to receive 8 weeks of treatment with escitalopram, sertraline, or extended-release venlafaxine (Etkin *et al.* 2015). Approximately one-quarter of patients had significant impairment across most cognitive tests relative to healthy control subjects, and these patients had poorer treatment outcomes. Worse cognitive task performance was associated with lower rates of remission (based on scores on the 16-item QIDS-SR), with 72%

accuracy for treatment with escitalopram but not for treatment with the other antidepressants. Among the patients predicted to be nonresponders, the greatest impairments were on tests of attention, decision speed, working memory, and speed of emotion identification. Those predicted to not achieve remission with escitalopram had a slightly higher score on the Ham-D (23.3 vs. 21.5). One interpretation of the results is that individuals with a greater level of cognitive impairment due to depression have poorer outcomes, which is not surprising. However, it does suggest that SSRI monotherapy, particularly with a highly selective serotonin reuptake inhibitor, may not be the best choice for patients with significant cognitive problems associated with depression.

Neuroimaging studies have also focused on identifying patterns of brain activation that may be predictive of antidepressant treatment outcomes. Previous functional MRI studies demonstrated that activation of the right lateral and medial prefrontal cortices and limbic regions during inhibitory responses on the go/no-go task predicted a greater treatment response to escitalopram (Langenecker *et al.* 2007). A similar approach was described in a study from the iSPOT-D trial that involved 80 medication-free outpatients with MDD and 34 matched healthy control subjects (Gyurak *et al.* 2016). During the functional MRI scans, patients completed three tasks to assess core domains of cognitive function. They then received 8 weeks of antidepressant treatment, functional MRI scans were repeated, and depression remission was assessed with Ham-D scores. Intact activation of the frontoparietal network during inhibitory no-go responses predicted remission, particularly for individuals given the SSRIs escitalopram and sertraline. During the no-go responses, remitters showed the same pretreatment dorsolateral prefrontal cortex activation as control subjects, and nonremitters showed hypoactivation relative to control subjects. These study findings hold promise for identifying biomarkers that can help predict which patients are most likely to respond to citalopram and escitalopram treatment.

Genome-Based Therapeutic Drugs for Depression study. A genome-based approach to identifying genes associated with therapeutic response to escitalopram has also yielded interesting findings. As part of the Genome-Based Therapeutic Drugs for Depression (GENDEP) study, genome-wide association analysis examined 539,391 single-nucleotide polymorphisms to identify genes that underlie individual differences in antidepressant treatment response. The partially randomized, single-blind study examined DNA from unrelated patients of European ancestry assigned to receive 12 weeks of treatment with either escitalopram 10-30 mg/day (n = 394) or nortriptyline 50-150 mg/day (n = 312). Although no marker was associated at a genome-wide level of significance, escitalopram response was predicted at a suggestive level of significance ($P = 0.00049$) by a synonymous single-nucleotide polymorphism (rs1126757) in interleukin gene *IL11* (Uher *et al.* 2010). In addition, a targeted analysis of 72 a priori selected candidate genes identified an association between escitalopram response and a single-nucleotide polymorphism (rs7801617) in the gene encoding *IL6*, a close homolog of *IL11*. A follow-up epigenetic study examined variations in DNA methylation of *IL11* as predictors of antidepressant treatment response using a subset of participants randomly selected from the GENDEP study who received either escitalopram (n = 80) or nortriptyline (n = 33) (Powell *et al.* 2013). This study reported that DNA methylation levels on some cytosine-phosphate-guanine (CpG) islands predicted antidepressant treatment response and that an interaction between CpG island methylation and genotype at rs1126757 could also predict treatment response. These studies are some of the first to provide evidence that a genomic approach may be fruitful for identifying molecular biomarkers that can predict which patients will best respond to specific antidepressants. However, as with the associations of the 5-HT$_{2A}$ variants noted earlier (see "Mechanism of Action" section), the ultimate predictive power of methylation of rs1126757 was low.

Another investigation from the GENDEP study sought to identify gene expression differences present prior to treatment that could predict treatment response. This study examined leukocyte mRNA expression in healthy control subjects (n = 34) and patients with depression (n = 74) before and after 8 weeks of treatment with escitalopram or nortriptyline (Cattaneo *et al.* 2013). The analysis was limited to 15 candidate genes that belonged to one of three groups previously implicated in the pathogenesis of depression or putative mechanisms of action of antidepressants (GR function, inflammation, and neuroplasticity). Regarding predictors present prior to treatment, nonresponders had higher mRNA levels for *IL1*b (+ 33%), macrophage inhibiting factor (+ 48%), and tumor necrosis factor (+ 39%). A similar study using a nonoverlapping set of GENDEP subjects and focusing only on escitalopram treatment also found higher mRNA levels for tumor necrosis factor (+ 20%) in nonresponders (Powell *et al.* 2013).

A second aim of the study by Cattaneo *et al.* (2013) was to identify changes in gene expression occurring during the course of successful treatment that could point to potential targets of drug action. Successful antidepressant treatment was associated with increases in mRNA levels for *BDNF* (+ 48%) and VGF nerve growth factor inducible (+ 20%) as well as modest reductions in mRNA levels for *IL6* ([?] 9%) and FK506 binding protein 5 ([?] 11%). Taken together, these data indicate that the genes thought to serve as predictors of antidepressant response may be separate from the genes hypothesized to be altered by successful treatment. The authors also noted that with the exception of *IL6*, all gene expression differences were in the same direction for both escitalopram and nortriptyline despite their different mechanisms of action, suggesting that these gene expression changes reflect alterations in pathways common to the two antidepressants and not pathways selective to serotonergic or adrenergic neurotransmission (Cattaneo *et al.* 2013).

Combining Medications to Enhance Depression Outcomes Trial and related combination treatment trials.

There is strong evidence that most, or possibly all, effective antidepressant treatments target a limited set of mechanisms that involve actions on neurotrophins, resulting in the formation of regulatory synapses between neurons (Duman and Duman 2015). However, the path to those mechanisms varies considerably between medications. The SSRIs block the reuptake of serotonin, selective norepinephrine reuptake inhibitors do so for norepinephrine, bupropion increases synaptic norepinephrine and dopamine, and medications such as mirtazapine and vortioxetine block specific serotonin receptors. Therefore, combining medications could enhance the downstream effects. A commonly used treatment is the combination of SSRIs and bupropion. An important question, then, has been whether combining antidepressants with different mechanisms could either speed response or increase the rate of remission.

In an early test of this hypothesis, Nelson *et al.* (2004) found that a combination of fluoxetine 20 mg/day plus desipramine (a relatively selective norepinephrine reuptake inhibitor) dosed to achieve an adequate blood level was superior to either fluoxetine or desipramine monotherapy. Blier *et al.* (2009) compared the relative effectiveness of paroxetine, mirtazapine, or their combination in patients with MDD. The combination treatment produced a substantially higher remission rate at 6 weeks (43%) than either mirtazapine (19%) or paroxetine (26%) monotherapy. In a subsequent study, this same group reported that the combination of escitalopram and bupropion produced higher rates of remission. Combinations of citalopram and bupropion or venlafaxine plus mirtazapine were also tested in the STAR*D trial described earlier (see "Mechanism of Action" section) (Rush *et al.* 2006). These combinations were effective, but not more so than monotherapies at the same level of care. The STAR*D trial was followed by the Combining Medications to Enhance Depression Outcomes Trial (CO-MED), which compared escitalopram (up to 20 mg/day), sustained-release bupropion (up to 400 mg/day) plus escitalopram, and the combination of venlafaxine and mirtazapine as initial treatment in patients with moderate to severe MDD (N = 665). Response and remission rates at 12 weeks and 7 months did not differ between groups, and side effects were worse for the venlafaxine plus mirtazapine group than

for escitalopram monotherapy. A criticism of CO-MED was that the dosing of medications was not optimal (the mean dose of mirtazapine was only 20 mg/day) and, in the case of escitalopram, varied between groups (Blier 2012). Given the flaws in CO-MED, there is no firm conclusion about the effectiveness of initial treatment with combined antidepressant medications. However, that should not necessarily detract from using combined antidepressants in difficult-to-treat depression (i.e., inadequate response to one or more antidepressant monotherapies).

Depression in Children and Adolescents

Fluoxetine is currently the only FDA-approved medication for the treatment of depression in both children and adolescents (ages 8 years and older). Escitalopram was approved in 2009 for the treatment of depression in adolescents (ages 12-17 years) but not in younger children. In addition, the FDA has mandated the placement of black box warnings on product labels to indicate the potential for increased suicidality associated with the use of SSRIs in patients younger than 25 years. Importantly, a meta-analysis of pediatric trials conducted between 1988 and 2006 indicated that the benefits of antidepressant treatment in the young outweigh the risks (Bridge *et al.* 2007).

Citalopram

Only a limited number of clinical studies have examined the effectiveness of citalopram in the treatment of depression in youth. In one double-blind trial involving 174 children and adolescents (ages 7-17 years), citalopram (20 mg/day) showed a modest superiority over placebo in the treatment of depression (Wagner *et al.* 2004). Conversely, citalopram (10-40 mg/day) was not superior to placebo in a clinical trial involving 244 adolescents (ages 13-18 years) receiving treatment for 12 weeks (von Knorring *et al.* 2006). Clearly, additional clinical trials are required to establish the efficacy and safety of citalopram in the treatment of childhood depression.

Escitalopram

Several studies have addressed the effectiveness of escitalopram in the pediatric population. Escitalopram was shown to be effective in the treatment of depression in adolescents (ages 12-17 years) in a randomized, double-blind, placebo-controlled multicenter clinical trial (Emslie *et al.* 2009). In this study, the group given escitalopram 10-20 mg/day ($n = 155$), compared with the group given placebo ($n = 157$), had greater improvement based on change from baseline to week 8 in scores on the Children's

Depression Rating Scale-Revised (CDRS-R). In another randomized double-blind trial investigating treatment of MDD in children and adolescents (ages 6-17 years), those given escitalopram 10-20 mg/day (n = 131) did not improve significantly more than those given placebo (n = 133). However, in a post hoc analysis of just the adolescents (ages 12-17 years), those given escitalopram (n = 80), compared with placebo (n = 77), had significantly more improved CDRS-R scores from baseline to week 8 (Wagner *et al.* 2006). Finally, the long-term benefits of escitalopram treatment for depression in adolescents were demonstrated in an extension trial that enrolled a subset of the sample participating in the aforementioned Emslie *et al.* (2009) study. This double-blind 16-to 24-week trial (Findling *et al.* 2013) showed that in comparison with subjects given placebo (n = 40), those given escitalopram 10-20 mg/day (n = 37) showed a modest but statistically significantly greater improvement in CDRS-R scores from baseline on the lead-in study to treatment week 24 (8-week lead-in study plus 16-week extension) (P = 0.005).

Generalized Anxiety Disorder

Citalopram

One small case series indicated that citalopram might be effective in generalized anxiety disorder (Varia and Rauscher 2002). However, no large-scale randomized, double-blind clinical trials have examined the effectiveness of citalopram in the treatment of this disorder. As described next, all large-scale trials have focused on the use of escitalopram in the treatment of generalized anxiety disorder.

Escitalopram

The efficacy of escitalopram in the treatment of generalized anxiety disorder has been established in several randomized controlled clinical trials (Baldwin and Nair 2005). Escitalopram's effectiveness in acute treatment of generalized anxiety disorder was shown in three double-blind, placebo-controlled clinical trials that were also subjected to pooled analysis. These studies demonstrated that escitalopram (10-20 mg/day administered for 8-12 weeks) was superior to placebo (Davidson *et al.* 2004; Goodman *et al.* 2005; Stein *et al.* 2005). The efficacy of escitalopram (10-20 mg/day) in the long-term treatment of generalized anxiety disorder was demonstrated in two 24-week controlled clinical trials, one open label (Davidson *et al.* 2005) and the other double blind (Bielski *et al.* 2005). Escitalopram also showed efficacy in the prevention of generalized anxiety disorder relapse for an additional 24-76 weeks (Allgulander *et al.* 2006). Escitalopram received FDA approval for generalized anxiety disorder in 2003.

Panic Disorder

Citalopram

Few well-controlled studies have evaluated the effectiveness of citalopram in the treatment of panic disorder. In a 1-year placebo-controlled, double-blind study of 279 patients who agreed to continue treatment after an acute period during which they were randomly assigned to citalopram (20 or 30 mg/day vs. 40 or 60 mg/day), clomipramine (60 or 90 mg/day), or placebo, all drug-treated groups showed significantly greater improvement compared with placebo on a variety of anxiety rating instruments, including the Clinical Anxiety Scale panic attack item. The authors concluded that citalopram at a dosage range of 20-60 mg/day was an effective long-term therapy for the management of panic disorder (Lepola *et al.* 1998).

Escitalopram

Escitalopram 5-10 mg/day was shown to be effective in the treatment of panic disorder in a 10-week randomized, double-blind, placebo-controlled, flexible-dosage study in patients with a diagnosis of panic disorder with or without agoraphobia (Stahl *et al.* 2003). Relative panic attack frequency was significantly lower in the escitalopram group (n = 125) than in the placebo group (n = 114). At the end of the study, a greater proportion of patients had zero panic attacks in the escitalopram group (50%) than in the placebo group (38%) ($P = 0.051$).

Social Anxiety Disorder

Citalopram

A large-scale, double-blind, placebo-controlled study demonstrated that paroxetine is effective for social anxiety disorder, suggesting that some SSRIs may be effective for this disorder (Stein *et al.* 1998). Despite the lack of large-scale, placebo-controlled studies using citalopram, case reports indicate that citalopram may be effective in the treatment of social anxiety disorder (Bouwer and Stein 1998; Lepola *et al.* 1994; Simon *et al.* 2001). In addition, one 12-week small-scale (*n* = 21), flexible-dose open-label study demonstrated the effectiveness of citalopram (20-60 mg/day) in relieving the symptoms of social anxiety disorder in patients with comorbid depression (Schneier *et al.* 2003).

Escitalopram

Two large-scale, multinational, multicenter clinical trials have demonstrated the effectiveness of escitalopram in the treatment of social anxiety disorder. In a 24-week fixed-dosage trial in patients with a diagnosis of social anxiety disorder, escitalopram at three dosages (5 mg/day, *n* = 167; 10 mg/day, *n* = 167; or 20 mg/day, *n* = 170) and paroxetine (20 mg/day, *n* = 169) each showed a statistically superior therapeutic effect compared with placebo (*n* = 166) by week 12 (Lader *et al.* 2004). Further improvement was seen by week 24 for all dosages of escitalopram and for paroxetine, and escitalopram 20 mg/day was superior to paroxetine 20 mg/day. In a 12-week study, escitalopram 10-20 mg/day (*n* = 181) produced a superior therapeutic response compared with placebo (*n* = 177) based on mean change in Liebowitz Social Anxiety Scale score from baseline (Kasper *et al.* 2005). Similar results were found in a large-scale study (*N* = 588) conducted in Japan (Asakura *et al.* 2016). In a long-term study, escitalopram treatment at a dosage of 10 or 20 mg/day for up to 24 weeks was shown to be effective in preventing relapse of social anxiety disorder after successful short-term therapy, with relapse being 2.8 times more likely with placebo treatment (*n* = 181) than with escitalopram treatment (*n* = 190) (Montgomery *et al.* 2005).

Anxiety Associated With Major Depressive Disorder

Citalopram

A retrospective study of 2,000 patients with depression enrolled in eight double-blind, placebo-controlled clinical trials revealed that citalopram was effective in relieving anxiety symptoms in patients with depression based on a greater decrease from baseline in the Ham-D anxiety factor (Flicker *et al.* 1998). The antidepressant effect in that study was equivalent in patients with MDD with higher and lower levels of anxiety. Another double-blind, placebo-controlled study in 323 patients with a diagnosis of MDD revealed a significant antianxiety effect of citalopram 20-60 mg/day compared with placebo based on decreases in Hamilton Anxiety Scale scores (Stahl 2000). In neither study was the effect on anxiety symptoms shown to be independent of improvements in depression, suggesting that the benefits were syndromic with regard to the depressive disorder.

Escitalopram

The effectiveness of escitalopram in the treatment of anxiety symptoms associated with MDD was evaluated in a pooled analysis of five clinical trials (Bandelow *et al.* 2007). These placebo-controlled trials were originally designed to examine the effectiveness of

escitalopram in treating MDD. In the pooled analysis, escitalopram 10-20 mg/day (*n* = 850) was consistently superior to placebo (*n* = 737) in relieving anxious symptoms associated with depression, as evaluated with several different assessments of anxiousness. The analyses presented in this pooled study indicate that escitalopram is effective in relieving anxiety symptoms in patients with depression. Like citalopram, there was not an independent effect on change in anxiety severity relative to change in depression.

Obsessive-Compulsive Disorder

Citalopram

To date, a limited number of clinical studies have evaluated the effectiveness of citalopram in the treatment of OCD. In the only published large-scale (*N* = 401), double-blind, placebo-controlled study of citalopram in the treatment of OCD, all three dosages of citalopram (20, 40, and 60 mg/day) given for 12 weeks were significantly more effective than placebo in relieving OCD symptoms (Montgomery *et al.* 2001). Another trial compared citalopram (60 mg/day) plus quetiapine (300-450 mg/day) with citalopram monotherapy (*N* = 76) and found that combined treatment was more effective than monotherapy. A secondary analysis of a clinical trial comparing citalopram with placebo identified five symptom clusters from the Yale-Brown Obsessive Compulsive Scale: contamination/cleaning, harm/checking, aggressive/sexual/religious, hoarding/symmetry, and somatic/hypochondria. Citalopram was more effective than placebo in reducing scores on most dimensions; patients who initially scored high on the hoarding/symmetry and contamination/cleaning factors did less well with citalopram. By contrast, people who initially scored higher on the aggressive/sexual/religious subscale did better with citalopram (Stein *et al.* 2007a). The relatively lower effect in patients with high hoarding scores is consistent with some prior research with SSRIs (Mataix-Cols *et al.* 1999).

Escitalopram

The effectiveness of escitalopram in the treatment of OCD was demonstrated in a 24-week double-blind, placebo-controlled, multicenter clinical trial (Stein *et al.* 2007b). In this study, escitalopram 20 mg/day (*n* = 116) and paroxetine 40 mg/day (*n* = 119) produced significant improvement compared with placebo; by week 24, all treatments, including escitalopram 10 mg/day (*n* = 116), were superior to placebo (*n* = 115). Long-term treatment with escitalopram was shown in one large-scale study to prevent relapse of OCD in patients who had responded to initial treatment (Fineberg *et al.* 2007). Patients treated with escitalopram 10 or 20 mg/day (*n* = 163) showed a significantly greater time to relapse compared with those receiving placebo (*n* = 157). A small randomized study found no differences between escitalopram and sertraline for OCD (Mowla *et al.* 2018).

Investigational Uses

Stress-Induced Myocardial Ischemia

Escitalopram

Substantial evidence implicates emotional stress as a trigger of acute coronary syndromes, and this effect can be reproduced in laboratory settings. Studies show that up to

70% of patients with stable coronary heart disease display mental stress-induced myocardial ischemia (MSIMI) (Strike and Steptoe 2003). The Responses of Mental Stress-Induced Myocardial Ischemia to Escitalopram Treatment (REMIT) study was designed to determine whether SSRI treatment could improve heart function after mental stress in patients with laboratory-diagnosed MSIMI. At the end of this 6-week randomized, double-blind, placebo-controlled study, significantly more patients receiving escitalopram treatment (*n* = 56; 5 mg/day titrated to 20 mg/day over 3 weeks) showed no MSIMI during three mental stressor tasks than those receiving placebo (*n* = 56) (OR, 2.62; 95% CI, 1.06-6.44; *P* = 0.04) (Jiang *et al.* 2013). There was no statistically significant effect for exercise-induced ischemia in the REMIT study. These results offer a preliminary indication of the potential utility of SSRIs in preventing mental stress-induced acute coronary syndromes.

Alzheimer's Disease

Citalopram

Brain accumulation of amyloid plaques formed by the aggregation of the amyloid-b peptide (Ab) is thought to be central to the pathophysiology of

Alzheimer's disease (Holtzman *et al.* 2011). The aggregation of Ab into plaques is concentration dependent (Bero *et al.* 2011; Lomakin *et al.* 1997); therefore, methods to decrease Ab levels may be therapeutic. Previous studies have shown that serotonin signaling suppresses the generation of Ab in vitro and in animal models of Alzheimer's disease (Cirrito *et al.* 2011; Nitsch *et al.* 1996). In an aged transgenic Alzheimer's disease mouse model (APP/PS1 plaque-bearing mice), acute citalopram treatment led to a dose-dependent decrease in brain interstitial fluid Ab levels, and chronic citalopram treatment arrested the growth of preexisting plaques and reduced the appearance of new plaques by 78% (Sheline *et al.* 2014). In addition, acute administration of citalopram (60 mg/day) in 23 healthy humans (ages 18-50 years; 11 female participants) in a double-blind study resulted in lower cerebrospinal fluid Ab production (37%) and concentration (38%) compared with placebo (Sheline *et al.* 2014). A similar effect was shown in aged mice with Alzheimer's disease. These results were supported in both mice and humans with other SSRIs (Cirrito *et al.* 2011). To the extent that Alzheimer's disease involves the accumulation of Ab, these results suggest a potential role for SSRI treatment in the prevention of Alzheimer's disease, and future studies should be aimed at defining the mechanism by which SSRI treatment lowers Ab levels.

Side Effects and Toxicology

Citalopram

In a meta-analysis of 746 patients with depression involved in several short-term clinical trials, the most common adverse events associated with citalopram were nausea and vomiting (20%), increased sweating (18%), and dry mouth and headache (17%) (Muldoon 1996). Analysis of an integrated safety database, which included data from 3,107 patients enrolled in 24 clinical trials, indicated that in placebo-controlled trials, nausea, dry mouth, somnolence, increased sweating, tremor, diarrhea, and ejaculatory failure of mild to moderate severity occurred with significantly greater frequency in patients given citalopram than in those given placebo (Muldoon 1996). The incidence of these adverse events with citalopram was less than 10% above that seen with placebo and was comparable to that reported with other SSRIs. Citalopram had a tolerability that was superior to that of the tricyclic antidepressants, with the exception that nausea and ejaculatory failure occurred with a 5% greater frequency in patients given citalopram (Keller 2000).

Escitalopram

In general, the side effects associated with escitalopram are similar to those observed with citalopram. In three placebo-controlled clinical trials performed with escitalopram, rates of discontinuation because of adverse events did not differ for patients given 10 mg/day compared with those administered placebo (Burke *et al.* 2002; Montgomery *et al.* 2001; Wade *et al.* 2002). In the trial that included an escitalopram dosage of 20 mg/day, the rate of discontinuation was 10.4% for the escitalopram-treated group versus 2.5% for the placebo-treated group (Burke *et al.* 2002). In addition, the rate of adverse events overall in the group receiving escitalopram 20 mg/day (85.6%) was significantly greater than that in the placebo group (70.5%). Regardless of dosage, the adverse events reported to occur more frequently with escitalopram compared with placebo are nausea, diarrhea, insomnia, dry mouth, and ejaculatory disorder, with nausea being reported most frequently at a rate of 15% (McRae 2002). To date, no published studies have reported clinically significant findings in laboratory test values, vital signs, weight gain or loss, or electrocardiogram values. Notably, sexual side effects in registration trials of citalopram and escitalopram (as well as other SSRIs) relied on self-report, which was likely to have underestimated the actual rate. Complaints of loss of libido, erectile dysfunction, and anorgasmia are common in patients treated with SSRIs. Sexual satisfaction tends to be low in the majority of patients with MDD and, even with SSRIs, improves with remission, although it tends to worsen for patients with nonremitting depression (Clayton *et al.* 2007; Ishak *et al.* 2013). Low sexual satisfaction and particularly worsened satisfaction may be an indicator of nonremission in SSRI-treated patients.

Specific Effects and Syndromes

QT Interval Prolongation

Citalopram is associated with a dose-dependent prolongation of the electrocardiographic corrected QT (QTc) interval, which can increase the risk of a potentially fatal abnormal heart rhythm called torsades de pointes, a type of polymorphic tachycardia. As a result, the FDA recommended that citalopram not be prescribed at dosages greater than 40 mg/day for most adults or greater than 20 mg/day for patients older than age 60 years (Medical Letter on Drugs and Therapeutics 2013; U.S. Food and Drug Administration 2017). In addition, citalopram use should be avoided in populations at increased risk for QTc interval prolongation, such as patients with congenital long QT syndrome. For at-risk patients for whom no satisfactory alternatives to citalopram are available, a low citalopram dosage should be used and electrocardiograms and/or electrolytes should be monitored. However, given the number of SSRIs currently available, citalopram should be avoided for higher-risk patients. Citalopram should be discontinued for patients with a QTc interval greater than 500 milliseconds. As in any clinical situation, the clinician must weigh the risk/benefit ratio for the treatment. In some cases, it may be reasonable to use dosages that exceed the FDA guidelines for patients with a lower risk for adverse effects. Importantly, escitalopram at dosages therapeutically equivalent to those of citalopram has not been demonstrated to significantly affect the QTc interval in most trials. However, one study in healthy control subjects (*N* = 40) reported a modest average increase of 10.5 milliseconds in patients treated with escitalopram 20 mg/day (Kim *et al.* 2016). This level of QTc prolongation is not considered clinically serious (Shah 2002). Escitalopram was also evaluated in a 24-week study in patients with depression and acute coronary syndrome; the escitalopram group had a lower rate of major adverse cardiac events relative to placebo-treated patients (Kim *et al.* 2018).

Hyponatremia

Citalopram and escitalopram have been shown to produce hyponatremia in case reports involving elderly patients, and this information has been reviewed elsewhere (Jacob and Spinler 2006). In addition to advanced age, other factors that may increase the likelihood of hyponatremia include female sex, concurrent diuretic use, low body weight, and recent pneumonia. Treatment of SSRI-induced hyponatremia usually involves fluid restriction and/or administration of a loop diuretic such as furosemide and may include discontinuation of the SSRI.

Discontinuation Syndrome

The abrupt cessation of antidepressant therapy can result in a discontinuation syndrome characterized by dizziness, nausea, vomiting, lethargy, and flulike symptoms (Shelton 2006). This syndrome is more common with shorter-half-life SSRIs or serotonin-norepinephrine reuptake inhibitors (e.g., paroxetine or venlafaxine) and is less common with longer-half-life SSRIs (e.g., fluoxetine). The data obtained from clinical trials suggest that the adverse events associated with discontinuation of citalopram or escitalopram tend to be mild and transient (Baldwin *et al.* 2007; Markowitz *et al.* 2000; Montgomery *et al.* 1993). However, dosage tapering rather than abrupt discontinuation is recommended for patients stopping treatment. In addition, patients should be warned of discontinuation symptoms during treatment should they miss doses or stop abruptly during treatment or when the medication is being tapered.

Treatment-Emergent Suicidal Ideation and Suicide

Considerable attention has been focused in recent years on the possibility that antidepressant drugs, especially SSRIs, may lead to treatment-emergent suicidal ideation (TESI) and an increased risk of suicide among some patients, particularly at the onset of therapy (Jick *et al.* 2004). This issue is of great concern for young patients and was described previously (see "Depression in Children and Adolescents"). In the case of citalopram, analyses of data obtained from 17 controlled clinical trials involving 5,000 patients indicate that the group receiving citalopram had a lower rate of suicide compared with the groups receiving placebo, tricyclic antidepressants, or other SSRIs (Nemeroff 2003). The risk of suicide associated with escitalopram was evaluated from data contained in the Summary Basis of Approval reports obtained from the FDA

(Khan and Schwartz 2007). The study authors did not detect a significantly greater rate of suicide in the escitalopram group compared with either the citalopram or placebo group. A meta-analysis of the escitalopram clinical trials database--consisting of 2,277 escitalopram-treated patients and 1,814 placebo-treated patients--also yielded no indication that escitalopram increased suicidal behavior in individuals with MDD and anxiety disorders (Pedersen 2005).

Although the data do not indicate a significantly greater risk of suicide for patients receiving either citalopram or escitalopram compared with those receiving placebo, most antidepressant studies show that a limited number of patients will exhibit TESI on initiation of therapy. Family and twin studies provide some evidence of a genetic influence on suicidal behavior, and it has been postulated that TESI may also be genetically influenced. Interestingly, a study in patients participating in the STAR*D trial demonstrated a significant association between citalopram-induced TESI in men and polymorphisms near the gene encoding cyclic adenosine monophosphate response element binding protein (*CREB*) (Perlis *et al.* 2007). This protein is of great interest because it mediates the effects of second messengers on new gene transcription and has been implicated in antidepressant action and suicide (Dowlatshahi *et al.* 1998; Dwivedi *et al.* 2003a). An analysis of nine candidate genes in patients from the GENDEP study who received either escitalopram or nortriptyline identified polymorphisms in *BDNF* as being associated with TESI, and there was also a significant interaction between variants in *BDNF* and *TRKB*, which encodes the BDNF receptor (Perroud *et al.* 2009). A proposed role for the *BDNF* pathway in TESI is consistent with previous reports of lower levels of *BDNF* mRNA and protein in the hippocampus and prefrontal cortex of individuals who died from suicide and lower levels of BDNF protein in the plasma of those who attempted suicide (Dwivedi *et al.* 2003b; Karege *et al.* 2005; Kim *et al.* 2007). In addition, *CREB* is thought to control *BDNF* gene transcription, providing a functional link between these two genetic associations and TESI (Dwivedi *et al.* 2003a; Finkbeiner 2000).

Finally, in a genome-wide association study also using GENDEP study participants, the strongest association with TESI was found for a single-nucleotide polymorphism located 30 kb downstream of the gene encoding guanine deaminase (Perroud *et al.* 2012). Investigators also found two suggestive escitalopram-specific associations with TESI that were contained in the gene for voltage-gated potassium channel-interacting protein 4 and near the gene for elongation protein 3 homolog (Perroud *et al.* 2012). Although no definitive conclusions can be drawn from this study or other genetic studies until they are replicated with larger samples, these findings point to the possibility that genetic markers may be used in the future to predict not only treatment response but also vulnerabilities to the adverse effects of specific drugs.

Drug-Drug Interactions

The majority of a citalopram dose is metabolized in the liver (75%). Yet because multiple CYP enzymes (CYP2C19, CYP3A4, and CYP2D6) contribute equally to the metabolism of citalopram and escitalopram, inhibition of metabolism by another drug of any one of these enzymes is unlikely to significantly affect the overall metabolism of citalopram or escitalopram. Consistent with this, there are relatively few reports in the literature of drug-drug interactions involving citalopram or escitalopram. Similarly, a loss-of-function genetic variation in one or two enzymes is unlikely to affect overall metabolism much. By contrast, a gain-of-function genetic variant, such as having multiple copies of *CYP2D6*, can adversely affect blood levels (Shelton *et al.* 2020). Because of the possibility of a potentially fatal pharmacodynamic interaction resulting in serotonin syndrome, neither citalopram nor escitalopram (or any SSRI or serotonin-norepinephrine reuptake inhibitor) should be administered with or within 14 days of discontinuing a monoamine oxidase inhibitor.

Conclusion

Citalopram and escitalopram are highly selective serotonin reuptake inhibitors that are well tolerated and effective for the treatment of depression, with escitalopram also having proven efficacy in large-scale clinical trials in the treatment of generalized anxiety disorder. Although the use of citalopram and escitalopram in the treatment of other psychiatric conditions has not been as thoroughly studied, the few well-controlled trials completed to date suggest that both drugs may have a role in treating other disorders, including panic disorder, social anxiety disorder, anxiety associated with depression, and OCD. However, neither drug is FDA approved for these indications. Citalopram and escitalopram rank among the most commonly prescribed medications. An advantage of citalopram and escitalopram compared with some other common SSRIs is a relatively weak inhibition of liver CYP enzymes, which reduces the potential for adverse pharmacokinetic drug-drug interactions. Citalopram has lower, and escitalopram much lower, protein binding than other SSRIs, making them safer when used with highly protein-bound drugs (e.g., warfarin); however, they are not as safe as venlafaxine and desvenlafaxine, which have very low protein binding. In addition, because escitalopram does not share with citalopram a modest affinity for the histamine$_1$ receptor, it may have a lower potential for antihistaminergic side effects compared with citalopram, a difference that has yet to be demonstrated in a clinical trial. In terms of effects on cardiac function, escitalopram's risk of producing QT interval prolongation appears to be lower than that of citalopram, and careful monitoring must accompany citalopram use for patients at risk for QT prolongation. A number of clinical trials have compared escitalopram with a variety of other antidepressants, including citalopram and venlafaxine, and suggest that escitalopram may have modest superiority in the treatment of individuals with severe depression. However, a clinically significant superiority of escitalopram over citalopram or other antidepressants in the "real world" of psychiatric practice is not established.

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CHAPTER 15

Trazodone and Nefazodone

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Trazodone was among the earliest "second-generation" antidepressants to become available for clinical use in the United States in the early 1980s. Its side-effect profile and potential toxicity were considerably different from--and in many instances preferable to--those of the original tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Several years later, trazodone's pharmacological "cousin," nefazodone, became available.

Trazodone

History and Discovery

Trazodone was first synthesized in Italy, and clinical studies began in the United States in 1978. In sharp contrast with most other antidepressants available at the time, trazodone showed minimal effects on muscarinic cholinergic receptors.

In 1982, trazodone was introduced for clinical use in the United States under the brand name Desyrel. Bioequivalent generic formulations are available for all tablet strengths. An extended-release preparation of trazodone (Oleptro) was removed from the U.S. market and is no longer available, and no liquid (solution or suspension) trazodone dosage form is currently marketed in the United States.

Structure-Activity Relations and Pharmacological Profile

Trazodone is a relatively weak selective serotonin reuptake inhibitor (SSRI); however, it is relatively *specific* for serotonin uptake inhibition, with minimal effects on norepinephrine or dopamine reuptake (Hyttel 1982) (Figure 15-1). Trazodone increases extracellular serotonin concentrations through a combination of mechanisms involving the serotonin transporter and the serotonin$_{2A/2C}$ receptors. In addition, trazodone has some serotonin receptor antagonist activity (Haria *et al.* 1994). Its active metabolite, *m*-chlorophenylpiperazine (m-CPP), is a potent direct serotonin receptor agonist. Thus, trazodone can be viewed as a mixed serotonergic agonist-antagonist, with the relative amount of m-CPP accumulation affecting the degree of predominant agonist activity. Sustained administration is associated with enhanced serotonergic neurotransmission in vivo in the rat brain (Ghanbari *et al.* 2010).

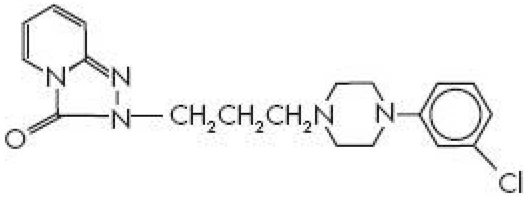

FIGURE 15-1. Chemical structure of trazodone.

In vivo, trazodone is virtually devoid of anticholinergic activity; in clinical studies, the incidence of anticholinergic side effects is similar to placebo. Trazodone is a relatively potent antagonist of postsynaptic a_1-adrenergic receptors and has a propensity to cause orthostatic hypotension. Trazodone has moderate antihistaminergic (histamine$_1$ receptor) activity.

Pharmacokinetics and Disposition

Trazodone is well absorbed after oral administration, with peak blood levels occurring about 1-2 hours after dosing. Trazodone is 89%-95% bound to plasma protein. Elimination appears to be biphasic; the initial a and subsequent b phases have half-lives of 3-6 and 5-9 hours, respectively. Bioavailability is not influenced by age or food intake.

Trazodone undergoes extensive hepatic metabolism. The active metabolite m-CPP is cleared more slowly than the parent compound (4-to 14-hour half-life) and reaches higher concentrations in the brain than in plasma (Caccia *et al.* 1981). The cytochrome P450 (CYP) 2D6 and CYP3A4 microsomal enzyme systems play a role in trazodone metabolism. The relation between steady-state trazodone blood levels and clinical response is not defined.

Mechanism of Action

The ultimate mechanism of action of trazodone remains unclear. Although the drug is described as a serotonin reuptake inhibitor, its effects on this neurotransmitter system are complex. Trazodone has relative selectivity for serotonin reuptake sites (Hyttel 1982); however, in vivo, it blocks the head twitch response induced by classic serotonin agonists in animals. The potent serotonin receptor agonist properties of trazodone's major metabolite, m-CPP, may play a role in the mechanism of action. Trazodone, unlike most antidepressants, does not produce downregulation of b-adrenergic receptors in the rat cortex (Sulser 1983).

Indications and Efficacy

The primary indication for trazodone is treatment of major depressive disorder (MDD). Early reviews found that trazodone's antidepressive efficacy was similar to that of the TCAs and the tetracyclic mianserin (Schatzberg 1987).

Questions have been raised about the effectiveness of trazodone in treating severely ill individuals with depression, especially those who have prominent psychomotor retardation. Shopsin *et al.* (1981) pointed out that in several unpublished double-blind, controlled studies, the rates of clinical response to trazodone were low (i.e., 10%-20%).

The performance of trazodone, in direct comparisons with other second-generation antidepressants, has been mixed. In a double-blind, placebo-controlled comparison with venlafaxine, response rates were 55% for placebo, 60% for trazodone, and 72% for venlafaxine. Trazodone was more effective than venlafaxine in ameliorating sleep disturbances but was associated with more dizziness and somnolence (Cunningham *et al.* 1994). In a double-blind comparison with bupropion, response rates were 46% for trazodone and 58% for bupropion (Weisler *et al.* 1994). In a double-blind study of 200 hospitalized patients experiencing a moderate to severe major depressive episode, mirtazapine yielded greater reductions in depression ratings than trazodone (van Moffaert *et al.* 1995). In a recent double-blind trial of extended-release venlafaxine versus once-a-day trazodone, both medications were effective in the treatment of MDD, with the trazodone formulation producing a statistically significant reduction in Hamilton Rating Scale for Depression scores by day 7 (Fagiolini *et al.* 2020).

Three double-blind studies reported that trazodone had antidepressant efficacy similar to that of other antidepressants in elderly patients (Gerner 1987). However, trazodone's association with orthostatic hypotension may increase the risk of falls, with devastating consequences for elderly patients. Trazodone is often helpful for geriatric patients with depression who have severe agitation and insomnia. A Cochrane Database Review found insufficient evidence to support trazodone as a treatment for the behavioral and psychological symptoms of dementia, although the review authors could not conclude that trazodone was ineffective, given the limited number of eligible studies (Martinon-Torres *et al.* 2004). In a study of 30 patients with Alzheimer's disease, trazodone normalized circadian rhythms (Grippe *et al.* 2015).

In a randomized, double-blind, placebo-controlled trial, the efficacy of trazodone was comparable to that of diazepam for generalized anxiety disorder, although diazepam treatment led to greater improvement in the first 2 weeks of treatment (Rickels *et al.* 1993).

Many clinicians use low-dosage trazodone as an alternative to benzodiazepines for the treatment of insomnia. At one point, trazodone was the second most prescribed agent for primary insomnia, even though there is minimal evidence to support its use for this indication (Mendelson 2005). In a recent meta-analysis, Yi *et al.* (2018) found trazodone to be effective in improving sleep maintenance by decreasing the number of early awakenings and enhancing perceived sleep quality, although there were no significant improvements in sleep efficiency. Yet the American Academy of Sleep Medicine clinical practice guideline does not recommend trazodone as a treatment for sleep onset or sleep maintenance insomnia (Sateia *et al.* 2017). Trazodone improved apnea-hypopnea index scores for patients with obstructive sleep apnea without any deleterious effects on oxygen saturation or non-rapid eye movement arousal threshold, suggesting that it might be beneficial in treating obstructive sleep apnea (Smales *et al.* 2015).

Trazodone is more effective than placebo when added to antipsychotic medication in the treatment of the negative symptoms of schizophrenia (Singh *et al.* 2010). A recent double-blind, placebo-controlled trial reported that trazodone was effective in treating antipsychotic-induced akathisia (Shams-Alizadeh *et al.* 2020).

Trazodone is commonly used off-label to treat a number of conditions, including bulimia nervosa, fibromyalgia, chronic pain, and diabetic neuropathy (Bossini *et al.* 2015). Adequately powered randomized controlled trials are needed to determine whether there is sufficient evidence to support trazodone's use for any of these indications.

Trazodone should be initiated at a low dosage and increased gradually, based on clinical response and tolerance to side effects. For the treatment of a major depressive episode, the suggested initial dosage is 150 mg/day, with increases of 50-mg increments every 3-4 days. Doses may be divided, but many patients prefer bedtime dosing because of the sedating effects. Although the maximum dosage recommended for outpatients is 400 mg/day, dosages up to 600 mg/day have been used for inpatients with more severe depression. When trazodone is prescribed as a hypnotic agent, the usual dose is 50 mg at bedtime, although some patients may require as little as 25 mg or as much as 200-300 mg.

Side Effects and Toxicology

Because of its lack of anticholinergic side effects, trazodone is especially useful for patients with prostatic hypertrophy, closed-angle glaucoma, or severe constipation. Trazodone's propensity to cause sedation is a double-edged sword. For many individuals, the relief from agitation, anxiety, and insomnia can be rapid; for others, including those with psychomotor retardation and low energy, trazodone may not be well tolerated.

Trazodone was among the top three medications associated with orthostatic hypotension in patients attending a Veterans Affairs geriatric clinic (Poon and Braun 2005). More than 200 cases of trazodone-associated priapism have been reported (Thompson *et al.* 1990), and the estimated incidence of abnormal erectile function is approximately 1 in 6,000 male patients. The risk appears to be greatest during the first month of treatment at low dosages (less than 150 mg/day). Early recognition of any abnormal erectile function is important and should prompt immediate discontinuation.

In overdose situations, trazodone appears to be *relatively* safer than TCAs, MAOIs, and a few of the other second-generation antidepressants, especially when it is the only agent taken. Fatalities are rare, and uneventful recoveries have been reported after ingestion of doses as high as 6,000-9,200 mg (Ayd 1984). When trazodone overdoses occur, clinicians should carefully monitor for hypotension.

Trazodone has the potential to impair driving skills, especially in new users, who have been shown to have an increased risk of motor vehicle crashes. The risk estimate for trazodone is roughly comparable to that of a blood alcohol concentration level of 0.09% (Hansen *et al.* 2015).

Drug-Drug Interactions

Trazodone can potentiate the effects of other CNS depressants. Patients should be warned about increased drowsiness and sedation when trazodone is combined with other CNS depressants, including alcohol.

The combination of trazodone with an MAOI, as with other antidepressants, should be handled with great caution, although there are case reports of successful combined use. Development of serotonin syndrome has been associated with the combination of trazodone with other pro-serotonergic agents. Trazodone inhibits the antihypertensive effects of clonidine. Trazodone can cause hypotension, especially orthostatic hypotension, and concomitant administration with antihypertensive therapy may require a reduction in the dosage of the antihypertensive agent.

Clinically significant cases of suspected trazodone-warfarin interactions have been described.

Nefazodone

History and Discovery

Trazodone's sedative properties and association with orthostatic hypotension inspired an effort to discover a modified molecule that would possess a more desirable pharmacological profile. This led to the development of nefazodone, which became available in the United States in 1994. Nefazodone and trazodone share a common active metabolite.

In 2004, the manufacturer of Serzone (nefazodone) announced that it was discontinuing the drug's sale in the United States, although generic nefazodone remains available. The drug had been banned in many countries because of its association with liver toxicity, and lawsuits against that manufacturer and the FDA were initiated in the United States.

Structure-Activity Relations and Pharmacological Profile

Nefazodone is a serotonin$_2$ (5-HT$_2$) receptor antagonist and a weak inhibitor of serotonin and norepinephrine reuptake (Figure 15-2). It has little affinity for a$_2$-adrenergic, b-adrenergic, or serotonin$_{1A}$ receptors, and its affinity for the a$_1$-adrenergic receptor is less than that of trazodone. Nefazodone is inactive at most other receptor-binding sites (Taylor *et al.* 1986).

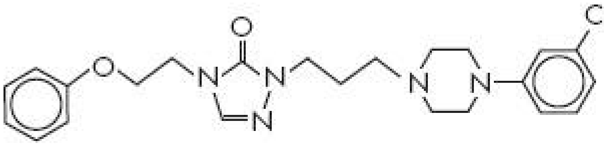

FIGURE 15-2. Chemical structure of nefazodone.

Pharmacokinetics and Disposition

Nefazodone is rapidly and completely absorbed and undergoes extensive first-pass metabolism, resulting in low (about 20%) and variable oral bioavailability. The plasma half-life is 2-4 hours. Nefazodone has three active metabolites: triazole dione, hydroxynefazodone,

and m-CPP. Triazole dione is a specific 5-HT$_2$ receptor antagonist with weaker affinity for that receptor than the parent compound and no appreciable effects on serotonin reuptake. With a plasma half-life of 18 hours, triazole dione predominates in the plasma, occurring at concentrations approaching four times those of the parent compound. Hydroxynefazodone has affinities for the 5-HT$_2$ receptor and serotonin reuptake site that are similar to those of the parent compound. Its plasma half-life is between 1.5 and 4 hours, and at steady state, plasma concentrations are approximately 40% of those of the parent compound. m-CPP is a direct agonist at the serotonin$_1$, 5-HT$_2$, and serotonin$_3$ receptors, with one-order-of-magnitude higher affinity for 5-HT$_{2C}$ receptors. m-CPP has a plasma half-life of 4-8 hours, and its plasma concentrations are only 7% of those seen with the parent compound (DeVane *et al.* 2002). However, the ratios of m-CPP to nefazodone concentrations in the brain are 47:1 and 10:1 in the mouse and rat, respectively. Brain concentrations of hydroxynefazodone in the rat are less than 10% of those in plasma, suggesting very poor blood-brain barrier penetration. Thus, despite its relatively lower plasma concentrations, m-CPP has a substantial presence in the brain, whereas the in vivo activity of hydroxynefazodone may be mostly the result of its biotransformation to m-CPP (Nacca *et al.* 1998).

Nefazodone has nonlinear kinetics, with greater than proportional mean plasma concentrations with higher dosages. Nefazodone is extensively (99%) but loosely protein bound (Teva Pharmaceuticals 2014). In patients with hepatic cirrhosis, single-dose nefazodone and hydroxynefazodone levels are about twice as high as in healthy volunteers (Barbhaiya *et al.* 1995).

Mechanism of Action

The mechanism of action of nefazodone is poorly understood. Nefazodone antagonizes 5-HT$_2$ receptors and inhibits reuptake of serotonin and norepinephrine (Teva Pharmaceuticals 2014). Several reviews refer to nefazodone as a "dual-acting" antidepressant, suggesting that it enhances both serotonergic and noradrenergic neurotransmission via uptake blockade. Although nefazodone has similar effects on the serotonin and norepinephrine transporters, this observation is potentially misleading. Nefazodone's inhibition of norepinephrine reuptake is weaker than that of the SSRI fluoxetine and is approximately three orders of magnitude weaker than what is seen with conventional norepinephrine reuptake inhibitors. Furthermore, nefazodone's inhibition of serotonin reuptake is nearly identical to that of desipramine and more than 100-fold less than that of fluoxetine (Bolden-Watson and Richelson 1993). Thus, the dual action of nefazodone refers to minimal, albeit equal, effects on serotonin and norepinephrine reuptake inhibition.

In humans, therapeutic dosages of nefazodone do not cause sustained serotonin uptake inhibition at the platelet serotonin transporter (Narayan *et al.* 1998). The active metabolite m-CCP, which appears to predominate in the brain because of greater penetration of the blood-brain barrier (Nacca *et al.* 1998), may play an important role in the mechanism of action.

Indications and Efficacy

In three of four Phase III imipramine-and placebo-controlled studies, nefazodone demonstrated similar efficacy to imipramine; in one of these studies, neither active drug had significantly greater efficacy than placebo (Rickels *et al.* 1995). The incidences of premature treatment discontinuation and side effects were higher for imipramine than for nefazodone (Rickels *et al.* 1995). In double-blind studies without placebo control groups, there were no significant differences between the clinical responses to nefazodone and sertraline or paroxetine in outpatients with depression (Feiger *et al.* 1996). Hospitalized patients with severe MDD had higher response rates to nefazodone compared with placebo (Feighner *et al.* 1998). In patients with moderate to severe MDD, the efficacy of amitriptyline was superior to that of nefazodone (Ansseau *et al.* 1994). Keller *et al.* (2000) compared nefazodone, cognitive-behavioral therapy (CBT), and their combination in a double-blind study of patients with chronic MDD. Each monotherapy yielded a response rate of 48%, whereas the combined treatment had greater efficacy (73%). In another study, depressed patients who did not respond to 12 weeks of treatment with either nefazodone or CBT achieved significant improvement when they were switched to the other treatment (Schatzberg *et al.* 2005). Nefazodone has demonstrated effectiveness in the continuation phase of treatment in double-blind studies (Baldwin *et al.* 2001).

In a double-blind, placebo-controlled study, nefazodone was safe and effective in the treatment of depression for patients with alcohol dependence, although it did not add any advantage over a psychoeducational group intervention in terms of drinking outcomes (Roy-Byrne *et al.* 2000). A double-blind controlled study reported that nefazodone was not efficacious for the treatment of alcohol dependence (Kranzler *et al.* 2000). A randomized, placebo-controlled, double-blind multicenter study compared nefazodone versus placebo and CBT versus nondirective group counseling (GC) for relapse prevention in alcohol dependence. Male patients (*n* = 242) received 1) nefazodone plus GC, 2) nefazodone plus CBT, 3) placebo plus GC, or 4) placebo plus CBT. There were no differences among the four groups in cumulative days of abstinence or amount of alcohol consumed during the initial 12-week study phase. After 1 year, the only significant difference among the groups was higher alcohol consumption in the nefazodone plus GC group, raising concerns that nefazodone may potentially increase the risk of relapse

(Wetzel *et al.* 2004). Other potential clinical applications for nefazodone have been explored, including treatment of PTSD (Jeffreys *et al.* 2012).

The usual starting dosage of nefazodone is 200 mg/day in two divided doses. The suggested dosage range is 300-600 mg/day. Increases should be in increments of 100-200 mg/day at weekly intervals. The starting dosage for elderly or debilitated patients should be lowered to 100 mg/day taken in two divided doses, and the rate of titration should be adjusted accordingly (Teva Pharmaceuticals 2014). Zajecka *et al.* (2002) reported that in studies comparing low-dosage (50-250 mg/day) and high-dosage (100-500 mg/day) nefazodone, better clinical response was obtained in the latter group, and the mean effective dosage ranged from 375 to 460 mg/day. A lower starting dosage should be considered when switching to nefazodone from an SSRI if a full washout has not been completed. Once-daily bedtime dosing appears to be well tolerated and effective.

Side Effects and Toxicology

In initial clinical trials that included approximately 2,250 patients, side effects more frequently associated with nefazodone than with placebo included dizziness, asthenia, dry mouth, nausea, and constipation (Fontaine 1993).

There are well-publicized concerns regarding the association of nefazodone with liver toxicity and liver failure, including fatalities (Voican *et al.* 2014). In 2001, the manufacturer added a black box warning to the nefazodone package insert, describing a reported rate of life-threatening liver failure in the United States of 1 case per 250,000-300,000 patient-years of nefazodone treatment. In 2004, Serzone was withdrawn from the U.S. market following its withdrawal from several international markets. The generic drug remains available in the United States.

Nefazodone appears to have advantages over SSRIs in terms of treatment-associated sexual dysfunction (Clayton *et al.* 2014). In a review of 1,338 individuals who experienced nefazodone overdoses, there were no reported deaths. The most common serious clinical effect was hypotension, reported in 1.6% of cases (Benson *et al.* 2000).

Drug-Drug Interactions

Increases in the plasma concentration of digoxin occur with concurrent nefazodone administration. Nefazodone increases the plasma concentrations of terfenadine and loratadine (with associated corrected QT prolongation), carbamazepine, and cyclosporine.

Conclusion

Trazodone was one of the earliest second-generation antidepressants. Its lack of anticholinergic effects provided an advantage over the TCAs for many patients. Its sedative properties are helpful for some patients but problematic for others. Orthostatic hypotension is a concern for elderly patients. Nefazodone and trazodone share an active metabolite, m-CPP, that may play an important role in their mechanism of action. The risk of serious liver damage led to the removal of Serzone from the market in several countries, although generic nefazodone is currently available in the United States.

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CHAPTER 16

Vortioxetine

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History and Discovery

Vortioxetine, formerly denoted Lu AA21004, was produced by Lundbeck in an attempt to add to a selective serotonin reuptake inhibitor (SSRI) additional properties, namely, serotonin (5-hydroxytryptamine [5-HT]) type 1A (5-HT_{1A}) and type 3 (5-HT_3) receptor affinities (Bang-Andersen *et al.* 2011). This was based on the premises that the antidepressant effect of SSRIs can be enhanced by combining them with a 5-HT_{1A} agonist and that 5-HT_3 antagonists are antiemetic drugs, with nausea being a common side effect of SSRIs (Sanchez *et al.* 2015). Eleven placebo-controlled studies for major depressive disorder (MDD) were conducted using a dosage ranging from 1 mg/day to 20 mg/day (Table 16-1); five of these studies included an active comparator group (venlafaxine in one study and duloxetine in the other four) (Sanchez *et al.* 2015). Vortioxetine was first approved in the United States and in Europe in 2013 for the treatment of MDD. Initially marketed under the brand name Brintellix, the drug was subsequently renamed Trintellix to avoid confusion with the anticoagulant Brilinta. No generic equivalent products are yet available, given that regulatory approval occurred relatively recently (Rudge 2021).

TABLE 16-1. Vortioxetine versus placebo/active comparator in acute studies ([?] 8 weeks) of depression

Study	Duration, *weeks*	Sample size, *N*	Vortioxetine dosage, mg/day (*n*)	Comparator used (*n*)	Comparator dosage, mg/day	Study results[a]	Findings

Study	Duration, *weeks*	Sample size, *N*	Vortioxetine dosage, mg/day (*n*)	Comparator used (*n*)	Comparator dosage, mg/day	Study results^a	Findings
Alvarez *et al.* 2012	6	429	5 (108) 10 (100)	Venlafaxine (112)	225	Positive	All groups > placebo
Henigsberg *et al.* 2012	8	560	1 (140) 5 (140) 10 (140)	None	--	Positive	All groups > placebo
Katona *et al.* 2012	8	453	5 (157)	Duloxetine (151)	60	Positive	Both groups separated from placebo
Jacobsen *et al.* 2015	8	462	10 (155) 20 (150)	None	--	Positive	Vortioxetine 10 mg/day did not separate from placebo
Boulenger *et al.* 2014	8	608	15 (149) 20 (151)	Duloxetine (146)	60	Positive	All groups > placebo
McIntyre *et al.* 2014	8	602	10 (195) 20 (207)	None	--	Positive	Both groups > placebo
Mahableshwarkar *et al.* 2015c	8	549	10-20 (175)	Duloxetine (187)	60	Positive	Both groups > placebo
Mahableshwarkar *et al.* 2015a	8	614	15 (147)	Duloxetine (152)	60	Positive	Vortioxetine 15 mg/day did not separate

Study	Duration, *weeks*	Sample size, *N*	Vortioxetine dosage, mg/day (*n*)	Comparator used (*n*)	Comparator dosage, mg/day	Study results[a]	Findings
			20 (152)				from placebo
Baldwin *et al.* 2012b	8	776	2.5 (155)	Duloxetine (155)	60	Failed	None of the groups separated from placebo
			5 (157)				
			10 (151)				
Jain *et al.* 2013	6	597	5 (299)	None	--	Failed	Vortioxetine did not separate from placebo
Mahableshwarkar *et al.* 2015b	8	469	10 (157)	None	--	Failed	Vortioxetine did not separate from placebo
			15 (152)				
Mahableshwarkar *et al.* 2013	8	611	2.5 (153)	Duloxetine (152)	60	Negative	Duloxetine separated from placebo, but vortioxetine did not
			5 (153)				

Note. > denotes a significantly greater effect.

[a] A positive study is one in which at least one vortioxetine arm separated statistically from placebo on the primary efficacy measure, a failed study is a trial in which the treatment group(s) did not separate from placebo, and a negative study is one in which the comparator separated from placebo but vortioxetine did not.

Source. Data from Sanchez *et al.* 2015.

Structure-Activity Relations

Vortioxetine is a piperazine derivative, and its chemical name is 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]-piperazine (Figure 16-1).

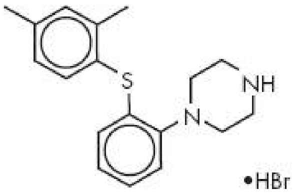

FIGURE 16-1. Chemical structure of vortioxetine.

The medication is produced in the form of a hydrobromide (HBr) salt.

Pharmacological Profile

Vortioxetine is described as a multimodal 5-HT agent because it acts on two types of neuronal elements: the 5-HT transporter and several 5-HT receptor subtypes. Among monoamine transporters, it binds selectively to the 5-HT transporter, but only to the same extent as other SSRIs at its maximal recommended regimen, as shown in PET studies in humans (Areberg *et al.* 2012; Meyer *et al.* 2004; Stenkrona *et al.* 2013). In order of affinity for human receptors, vortioxetine is a 5-HT transporter inhibitor, a 5-HT_3 antagonist, a full 5-HT_{1A} agonist, a 5-HT_7 antagonist, a partial 5-HT_{1B} agonist, and a 5-HT_{1D} antagonist (Mork *et al.* 2012). On the basis of plasma levels and affinity values, all of these targets could be engaged by vortioxetine to physiologically relevant levels within its usual therapeutic dosage range. Although the clinical significance of these various activities at 5-HT receptors in the presence of lower occupation of 5-HT transporters has not been determined, synergies between such neuronal elements on neurotransmitter levels have been documented in the brains of laboratory animals (Sanchez *et al.* 2015).

Pharmacokinetics and Disposition

The pharmacokinetics of vortioxetine are linear and dose proportional across a wide dosage range (2.5 mg-60 mg) when administered once daily. Vortioxetine is well absorbed (approximately 75%) from the gastrointestinal tract, and because its bioavailability is similar under fasting and fed conditions, it may be taken without regard to meals. It reaches a plasma peak in 7-11 hours, and it is 98% bound to plasma proteins. Vortioxetine is not a substrate for the permeability glycoproteins, which indicates that its brain levels will not be affected by possible polymorphisms of these efflux carriers. The terminal half-life of vortioxetine is about 66 hours, and steady-state concentrations are achieved after 2 weeks; consequently, complete elimination requires 2 weeks as well (Areberg *et al.* 2014; Bundgaard *et al.* 2016).

Metabolism

Vortioxetine is metabolized extensively through oxidation and subsequently by glucuronic conjugation. The cytochrome P450 (CYP) 2D6 isoenzyme is the main enzyme catalyzing its catabolism to its major carboxylic acid metabolite, which is pharmacologically inactive. About two-thirds of the inactive metabolites are excreted in the urine and the last third in the feces. Very small amounts of unchanged vortioxetine are excreted in the urine. No dosage adjustment is necessary in patients with renal impairment or mild to moderate hepatic impairment; however, vortioxetine is not recommended in patients with severe hepatic insufficiency. Plasma levels of vortioxetine are about 2 times higher in poor metabolizers of CYP2D6 and when it is administered with bupropion (Areberg *et al.* 2014; Chen *et al.* 2013).

Indication and Efficacy

The clinical development program for vortioxetine in MDD has been successful, and currently the only approved indication of vortioxetine worldwide is for the treatment of MDD.

To this day, 8 of 14 placebo-controlled short-term studies using change in the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979) as the primary endpoint have been positive (Alvarez *et al.* 2012; Baldwin *et al.* 2012a; Boulenger *et al.* 2014; Henigsberg *et al.* 2012; Inoue *et al.* 2018, 2020; Jacobsen *et al.* 2015; Jain *et al.* 2013; Mahableshwarkar *et al.* 2013, 2015a, 2015b; Nishimura *et al.* 2018; Wang *et al.* 2019), including one in elderly patients (Katona *et al.* 2012). There is also one double-blind maintenance study with a duration of 24 weeks that was positive (Boulenger *et al.* 2012), and there are five open-label studies over 52 weeks that assessed vortioxetine's safety, tolerability, and maintained effectiveness in patients with MDD treated with 5-10 mg/day (n = 1,313) or 15-20 mg/day (n = 1,144; Baldwin *et al.* 2016; Vieta *et al.* 2017).

Of the short-term studies, seven were active referenced (six duloxetine, one venlafaxine XR) (Borhannejad *et al.* 2020; Boulenger *et al.* 2012; Inoue *et al.* 2020; Koesters *et al.* 2017; Wang *et al.* 2019). Only one double-blind study examined the responsiveness to vortioxetine in 493 patients with MDD who had not responded adequately to an SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI) (Montgomery *et al.* 2014). In this study, patients were asked to decrease their current drug regimen to the minimal effective dosage in the week prior to their random assignment to either vortioxetine or the melatonin receptor agonist/5-HT$_{2B/2C}$ antagonist agomelatine. Both agents could be titrated to their maximal recommended doses. Vortioxetine was statistically superior to agomelatine.

Only two other studies have directly compared vortioxetine to another medication (sertraline and venlafaxine). In both cases, vortioxetine was not inferior to its comparator (Borhannejad *et al.* 2020; Wang *et al.* 2015).

A recent meta-analysis found 17 studies that used the MADRS as a primary or secondary endpoint with a total of 7,269 patients randomly assigned to either vortioxetine (3,630) or placebo (3,639) (Iovieno *et al.* 2021). This study found an overall standardized mean difference (SMD) of 0.33 (0.24-0.41) favoring vortioxetine, with increments in the SMD of 0.24 (0.08-0.39), 0.33 (0.19-0.47), 0.26 ([?]0.06 to 0.58), and 0.44 (0.27-0.62) for dosages of 5, 10, 15, and 20 mg/day, respectively. It is noteworthy that only three studies used the 15 mg/day dosage, which could account for the lack of statistical significance for this dosage.

A Cochrane systematic review and meta-analysis also concluded that vortioxetine may be more effective than placebo for response (Mantel-Haenszel RR, 1.35; 95% CI, 1.22-1.49; 14 studies, 6,220 participants), remission (RR 1.32; 95% CI, 1.15-1.53; 14 studies, 6,220 participants), and depressive symptoms (measured using the MADRS; mean deviation [MD], [?]2.94, 95% CI, [?]4.07 to [?]1.80; 14 studies, 5,566 participants [Koesters *et al.* 2017]).

On the basis of such results, the recommended effective dosage ranges from 5 mg/day to 20 mg/day. In adults ages 18-65 years, the usual recommended starting dosage is 10 mg/day; for convenience, vortioxetine is usually taken in the morning after a meal, but it can also be taken at night. In elderly patients, the starting dosage should be 5 mg/day. Although in controlled studies the dosage was commonly increased after 1 week, in clinical practice uptitration should occur after a minimum of 2 weeks, given that this is the time necessary to achieve a plasma steady-state level.

There have been four short-term placebo-controlled studies in generalized anxiety disorder (Bidzan *et al.* 2012; Mahableshwarkar *et al.* 2014a, 2014b; Rothschild *et al.* 2012) and one large relapse prevention trial (Baldwin *et al.* 2012b). Of these studies, one short-term trial (Bidzan *et al.* 2012) and the relapse prevention trial were positive (Baldwin *et al.* 2012b). However, in meta-analyses, vortioxetine did not separate from placebo for dosages of 2.5, 5, or 10 mg/day (Qin *et al.* 2019). Studies of higher dosages (i.e., 15 mg/day or 20 mg/day) would be interesting, as anxiety disorders generally respond to higher doses than depressive disorders. Although methodological issues may have been at play in the failed trials, there is not yet enough evidence to proceed with an indication of vortioxetine in generalized anxiety disorder.

On the basis of the premise that the pharmacological profile of vortioxetine could have beneficial effects on cognitive dysfunction in MDD, cognitive testing was included in many trials, either as the primary endpoint or as part of the secondary endpoints. The Digit Symbol Substitution Test (DSST; a pencil-and-paper task that assesses attention, speed of processing, and executive function) was most often used. Other cognitive tests used in trials of vortioxetine include the Rey Auditory Verbal Learning Test and the University of California

San Diego Performance-based Skills Assessment (UPSA). It is interesting that a functional MRI study found evidence supporting a direct effect of vortioxetine on neural circuitry in patients with remitted depression (Smith *et al.* 2018).

Initially three short-term trials examined cognitive function with a battery of tests, one in elderly patients and two with a primary outcome measure of improvement in cognitive function, and all three trials yielded positive antidepressant action over placebo (Katona *et al.* 2012; Mahableshwarkar *et al.* 2015c; McIntyre *et al.* 2014). Vortioxetine exerted a significantly greater effect over placebo on performance on the DSST in all three studies. In contrast, there was no significant effect of duloxetine (60 mg/day) over placebo on performance on the DSST in the two studies that used this medication as a comparator (Katona *et al.* 2012; Mahableshwarkar *et al.* 2015c). Furthermore, this beneficial action was deemed through path analysis to mostly be a direct effect independent of the antidepressant effect of vortioxetine. The effect of vortioxetine on cognition found in these three studies was confirmed in a random effects meta-analysis (McIntyre *et al.* 2016) as well as in a network meta-analysis, in which it was shown to be the only medication with antidepressant action to improve cognitive function scores on the DSST over placebo (Baune *et al.* 2018a). In more routine daily task testing (through the UPSA), vortioxetine but not duloxetine separated from placebo, with the difference being almost entirely attributable to a direct effect. These different findings led the European Medicines Agency, but not the U.S. FDA, to put in the label for vortioxetine a cognition claim for patients with MDD.

Since 2016, three other studies have used the DSST as a primary efficacy endpoint, but none showed a statistically significant difference from placebo or comparator, although all three supported vortioxetine as effective for the treatment of depression. Each of these studies had a specific focus and small sample size and thus lacked power. The first compared switching to vortioxetine or escitalopram in patients with inadequate response to their current antidepressant monotherapy (Vieta *et al.* 2018). The second studied the effects of adding vortioxetine versus placebo to the current treatment for patients in full or partial remission with residual cognitive symptoms (Nierenberg *et al.* 2019). The third compared vortioxetine to paroxetine or placebo in working patients with depression (Baune *et al.* 2018b).

Apart from the above studies in which improvement in cognitive function was the primary outcome measure, many other studies have investigated the cognitive effects of vortioxetine through secondary endpoints or post hoc analysis of patient populations of studies that had included various scales of cognitive, social, or workplace functioning with mixed but primarily positive results (Christensen *et al.* 2018; Harrison *et al.* 2016; Inoue *et al.* 2020; Jacobson *et al.* 2020; Keefe *et al.* 2018; Lee *et al.* 2018; McIntyre *et al.* 2017).

An interventional 52-week open-label study, AtWoRC (Assessment in Work productivity and the Relationship with Cognitive symptoms; Chokka *et al.* 2019), investigated the association between cognitive symptoms and workplace productivity in working patients with depression treated with vortioxetine (10-20 mg/day). This study found a significant correlation between the 20-item Perceived Deficits Questionnaire--Depression and the Work Limitations Questionnaire at both week 12 and week 52.

In recent years, studies have investigated vortioxetine in patients with other diagnoses. An open-label, flexible-dose study showed statistically significant improvement for panic disorder (Shah and Northcutt 2018). A randomized double-blind, placebo-controlled trial showed statistically significant improvement in negative symptoms of patients with chronic schizophrenia when vortioxetine was used in addition to risperidone 4-6 mg/day (Moazen-Zadeh *et al.* 2020). Also, vortioxetine significantly improved quality of life compared with placebo in a double-blind randomized controlled trial for patients with irritable bowel syndrome (Seddighnia *et al.* 2020). No statistically significant difference was found versus placebo for social anxiety disorder comorbid with depression (although there was a significant effect on the MADRS [Liebowitz *et al.* 2017]), ADHD (Biederman *et al.* 2019), binge-eating disorder (Grant *et al.* 2019), or PTSD (Dunlop *et al.* 2021).

Two studies investigated the effects of vortioxetine on cognition in patients with cognitive decline. One open-label observational 12-month study compared the effects of vortioxetine versus other medications with antidepressant properties (control group) on performance on the Mini-Mental State Examination (primary endpoint) and other cognitive tests among patients with mild Alzheimer's disease and depressive symptoms. This study showed that vortioxetine produced statistically significant improvement on the Mini-Mental State Examination and most cognitive tests, as well as on Hamilton Rating Scale for Depression scores and Cornell Scale for Depression in Dementia total scores (Cumbo *et al.* 2019). The other study evaluated the effects of adding vortioxetine versus placebo to a 26-week course of cognitive training for adults age 65 years and older with age-related cognitive decline. The primary outcome was global cognitive performance (using the National Institutes of Health Toolbox Cognition Battery

fluid cognition composite), on which vortioxetine separated from placebo only at the 12-week time point (Lenze *et al.* 2020).

Side Effects and Toxicology

The most common adverse reactions reported with vortioxetine use are nausea, constipation, and vomiting (Takeda Pharmaceuticals 2021). The main side effect of vortioxetine on treatment initiation is nausea. It occurs at about the same rate as with SSRIs and SNRIs, generally in about one-quarter to one-third of patients (Citrome 2014). This finding is somewhat surprising, as vortioxetine is a potent 5-HT$_3$ receptor antagonist, which should prevent any nausea resulting from 5-HT reuptake inhibition. However, nausea can be produced by a variety of mechanisms, such as opioid and dopamine receptor activation, b-human chorionic gonadotropin hormone, and, importantly, 5-HT$_{1A}$ receptor agonism (as with the 5-HT$_{1A}$ receptor agonist buspirone). The latter effect is likely responsible for the transient nausea often reported during the first 2 weeks of vortioxetine administration, given the potent 5-HT$_{1A}$ receptor agonism of vortioxetine. In an analysis of data from randomized placebo-controlled trials and open-label extension studies by Baldwin *et al.* (2016), this side effect was found to lead to discontinuation of treatment in 1%-4% of subjects and appeared to be dose dependent. Apart from these gastrointestinal side effects, other side effects reported in the vortioxetine group were generally not markedly different from those reported in the placebo group (Baldwin *et al.* 2016). Overall, discontinuation due to treatment-emergent adverse events was dose dependent and was between 4.5% and 8.5%, reaching the same level as with 60 mg/day of duloxetine, with the placebo rate being 3.5% (Baldwin *et al.* 2016). In a study comparing the treatment initiation of oral vortioxetine (10 mg/day) with an initial dose of intravenous vortioxetine versus intravenous placebo (Vieta *et al.* 2019), nausea was also the most common side effect, reported by 48% of the intravenous vortioxetine group versus 32% of the intravenous placebo group, with comparable severity between the two groups. In the intravenous vortioxetine group, nausea appeared within the first 2 days, with no new incidence after 2 days; the mean duration was 4.5 days, much shorter than the mean duration of 12.5 days in the placebo group (Vieta *et al.* 2019). When side effects are problematic, vortioxetine should be withheld for 3 days (given its long half-life) and restarted at half the prior daily dose.

Vortioxetine has not exerted clinically meaningful effects on body weight in short-term or long-term clinical studies. It has not been associated with an incidence of insomnia or daytime somnolence that is above the placebo level, unlike venlafaxine, which produces greater rates of insomnia, or duloxetine, which produces greater rates of somnolence. There are no significant discontinuation symptoms associated with abrupt cessation of vortioxetine, as is expected from its long terminal half-life.

Sexual dysfunction is a class side effect of drugs that potently inhibit the 5-HT transporter. Rates of sexual dysfunction (as measured on the Arizona Sexual Experiences Scale) among patients receiving vortioxetine 5 mg/day or 10 mg/day did not differ from rates for patients receiving placebo; however, for patients receiving vortioxetine 20 mg/day, rates of sexual dysfunction were equivalent to rates for patients receiving duloxetine 60 mg/day (Baldwin *et al.* 2016). These results are consistent with the lower occupation of the 5-HT transporter with vortioxetine at dosages lower than at 20 mg/day, which is about the same as with duloxetine 60 mg/day (i.e., 80% [Takano *et al.* 2006]). In one study, 477 patients with MDD who were responding to paroxetine, sertraline, or citalopram but experiencing treatment-emergent sexual dysfunction were switched to either vortioxetine or escitalopram (10 mg/day or 20 mg/day [Jacobsen *et al.* 2015]). Benefits of vortioxetine over escitalopram were significantly greater on four of five dimensions of the Changes in Sexual Functioning Questionnaire--Short Form and for all three phases of sexual functioning. Although the absolute difference between the two groups was significant, it is important to note that three-quarters of patients on vortioxetine were taking 20 mg/day.

No cases of vortioxetine overdose are reported in the literature. A supratherapeutic dosage of vortioxetine 40 mg/day for 14 days did not produce clinically relevant electrocardiography or hemodynamic changes (i.e., QTc prolongation of 5 ms [Wang *et al.* 2013]).

Drug-Drug Interactions

Vortioxetine must never be administered in combination with a monoamine oxidase inhibitor (MAOI). Before vortioxetine is started, there must be an elimination period of 14 days for an irreversible MAOI but only 2 days in the case of the reversible MAOI moclobemide. Similarly, there must be a 14-day elimination period of vortioxetine before either an irreversible MAOI or moclobemide is initiated.

Vortioxetine is not an inhibitor or an inducer of any metabolic enzymes. Consequently, it will not alter levels of other medications through metabolic interference. Complete inhibitors of CYP2D6, such as fluoxetine and paroxetine, as well as moderate inhibitors, such as bupropion and duloxetine, will approximately double the exposure (area under the curve) to vortioxetine. These interactions are expected to occur mainly in switch situations, which are discussed below. In such concomitant regimens, the dosage of vortioxetine should be reduced by half (D'Empaire *et al.* 2011; Hvenegaard *et al.* 2012).

Triptans for the treatment of migraines may be less effective in the presence of vortioxetine. This class of agents acts mainly by activating 5-HT$_{1D}$ receptors, whereas vortioxetine is a 5-HT$_{1D}$ receptor antagonist. However, because the affinity of vortioxetine for the 5-HT$_{1D}$ receptor is the lowest among all of the 5-HT neuronal elements (Mork *et al.* 2012), the activity of triptans may not be reduced at lower dosages of vortioxetine.

Strategies for Switching to Vortioxetine

Despite an extensive clinical program, there are actually only three studies that have reported on a switch to vortioxetine from other medications with antidepressant effects (Jacobsen *et al.* 2015; Mills *et al.* 2021; Montgomery *et al.* 2014). Although these patients seemed to tolerate the switch to vortioxetine well, in clinical practice switching has been more problematic. A likely explanation for patients prematurely stopping vortioxetine may stem more from the abrupt, or too rapid, interruption of the SSRI or SNRI than from vortioxetine itself. As illustrated in Figure 16-2, SSRIs or SNRIs are eliminated within

several days, which rapidly decreases the occupation of the 5-HT transporters, although a steady-state of vortioxetine is achieved only after 2 weeks, then producing about 60% occupancy at 10 mg/day and 80% at 20 mg/day. Consequently, discontinuation symptoms could occur during a rapid switch that could be exacerbated by the potent 5-HT$_{1A}$ agonistic profile of vortioxetine. It is thus recommended that a gradual crossover strategy be implemented when switching from SSRIs or SNRIs to vortioxetine. One exception would be a switch from fluoxetine because of its long half-life. However, because fluoxetine is a CYP2D6 inhibitor, the initial dosage of vortioxetine should be 5 mg/day, and the dosage should be gradually increased with the slow elimination of fluoxetine.

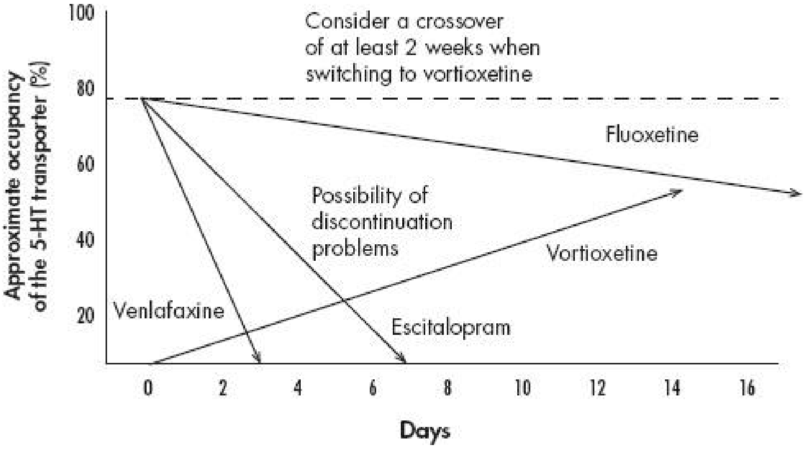

FIGURE 16-2. Relationship between serotonin transporter occupancy by various drugs used to treat depression and time following their discontinuation and the introduction of vortioxetine.

The *lines* represent the decrease in serotonin (5-HT) transporter occupancy following an abrupt cessation of the selective serotonin reuptake inhibitors escitalopram and fluoxetine and the serotonin-norepinephrine reuptake inhibitor venlafaxine (at their minimal effective doses) in comparison to the increase in 5-HT transporter occupancy following initiation of the multimodal agent vortioxetine at dosages of 5-10 mg/day. When most 5-HT reuptake inhibitors, with the exception of fluoxetine, are discontinued abruptly, discontinuation phenomena may be triggered, leading to an apparent intolerance of vortioxetine. Therefore, the ongoing medication should be decreased gradually while vortioxetine levels are building up.

Conclusion

Vortioxetine is a multimodal serotonergic agent that inhibits the 5-HT transporter, albeit to a lesser extent than other SSRIs, and has a variety of actions at five 5-HT receptor subtypes. Its only approved indication is for the treatment of MDD. Although it may produce as much mild to moderate nausea as SSRIs on treatment initiation, nausea is generally transient and seldom leads to discontinuation of treatment. At dosages of 10 mg/day or less, vortioxetine is expected to produce less sexual dysfunction than SSRIs and SNRIs. Vortioxetine does not impact the cardiovascular system, even at twice its maximal recommended dosage. Vortioxetine will not alter levels of other medications because it is not a hepatic enzyme inducer or inhibitor. It is still too early to determine its role in treatment-resistant depression. However, vortioxetine may exert a beneficial action on cognitive functioning in some patients with MDD.

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CHAPTER 17

Mirtazapine

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History and Discovery

Mirtazapine, originally known as ORG 3770, was first synthesized in the Netherlands by the Department of Medicinal Chemistry of NV Organon (Kaspersen *et al.* 1989). First approved for use in major depressive disorder (MDD) in the Netherlands in 1994, mirtazapine was introduced in the United States in 1996.

Structure-Activity Relations

Mirtazapine (Figure 17-1) is a member of the piperazinoazepines, a class of chemical compounds that is unrelated to any other medication class used in the treatment of psychiatric conditions (Maris *et al.* 1999). Mirtazapine is also known by its chemical name, 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c] benzazepine (Dahl *et al.* 1997; Dodd *et al.* 2000).

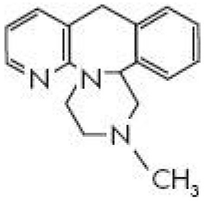

FIGURE 17-1. Chemical structure of mirtazapine.

Pharmacological Profile

Mirtazapine is described as a noradrenergic and specific serotonergic antidepressant (Holm and Markham 1999; Kent 2000; Nutt 1998). It is a potent serotonin$_2$ (5-HT$_2$), serotonin$_3$ (5-HT$_3$), and central a$_2$-adrenergic receptor antagonist (de Boer 1996; de Boer *et al.* 1995; Kooyman *et al.* 1994). Antagonism of 5-HT$_2$ and 5-HT$_3$ receptors results in an increase in serotonin$_{1A}$ (5-HT$_{1A}$) receptor-mediated transmission, thus exerting a more specific effect on serotonergic transmission, relative to the selective serotonin reuptake inhibitor (SSRI) class of antidepressants (Bengtsson *et al.* 2000; Berendsen and Broekkamp 1997; Kent 2000). In addition, because a$_2$-adrenergic receptors normally act to inhibit transmission at serotonergic and noradrenergic axon terminals, mirtazapine acts to increase the release of both serotonin (5-HT) and norepinephrine via blockade of central a$_2$ receptors (Numazawa *et al.* 1995).

Mirtazapine has no significant affinity for dopamine receptors, low affinity for muscarinic cholinergic receptors (de Boer 1996), and high affinity for histamine$_1$ receptors (de Boer 1996). Mirtazapine appears to have no effect on 5-HT and dopamine reuptake and only a minimal effect on norepinephrine reuptake (de Boer 1996; Kent 2000). The drug appears to significantly reduce cortisol levels (Laakmann *et al.* 2004; Schmid *et al.* 2006), an effect that has been demonstrated in both patients and healthy volunteers (Laakmann *et al.* 1999, 2003).

Pharmacokinetics and Disposition

Absorption

Mirtazapine is well absorbed from the gastrointestinal tract, and bioavailability does not appear to be affected by the presence of food in the stomach (Fawcett and Barkin 1998b). An oral rapidly disintegrating tablet has been available since 2001 (Benkert *et al.* 2006), along with immediate-release oral tablets. Generic equivalents are available for both dosage forms.

Distribution

Mirtazapine appears to be 85% bound to plasma proteins (Fawcett and Barkin 1998b).

Metabolism

Mirtazapine is primarily metabolized by the liver via demethylation and hydroxylation, followed by glucuronidation (Fawcett and Barkin 1998b; Merck and Co. 2020). A major metabolite, desmethylmirtazapine, and some minor metabolites are weakly active but are present in lower serum concentrations than the parent compound (Fawcett and Barkin 1998b; Kent 2000; Merck and Co. 2020). Mirtazapine lacks both autoinduction and autoinhibition of hepatic cytochrome P450 (CYP) enzymes (Fawcett and Barkin 1998b). Although in vitro studies do not demonstrate an inhibitory effect, mirtazapine is a substrate for CYP1A2, CYP2D6, and CYP3A4 (Fawcett and Barkin 1998b; Merck and Co. 2020). Mirtazapine is a mild competitive inhibitor of CYP2D6 (Barkin *et al.* 2000; Fawcett and Barkin 1998b). A pharmacogenetic study of CYP2D6 in older patients with depression did not show increased dropout rates for slow and intermediate metabolizers due to side effects of the drug (Murphy *et al.* 2003b). These findings suggest that mirtazapine is well tolerated in individuals who are slow metabolizers of CYP2D6.

Elimination

Mirtazapine and its metabolites are eliminated primarily in the urine (up to 75%) and feces (up to 15%; Fawcett and Barkin 1998b). The elimination half-life of mirtazapine is 20-40 hours (Fawcett and Barkin 1998b; Merck and Co. 2020; Stimmel *et al.* 1997). Of note, the clearance of mirtazapine may be affected by hepatic or renal impairment (Fawcett and Barkin 1998b). The elimination half-life may increase by 30%-40% in patients with hepatic impairment (Fawcett and Barkin 1998b; Kent 2000). In patients with moderate to severe renal impairment, the clearance of mirtazapine may be reduced by 30%-50% (Fawcett and Barkin 1998b; Kent 2000; Merck and Co. 2020). Although no dosage adjustments are recommended in the product labeling to compensate for renal or hepatic impairment, caution is advised.

Indications and Efficacy

Major Depressive Disorder

In a randomized, double-blind, placebo-controlled study of 90 outpatients with a major depressive episode, mirtazapine treatment resulted in clinically significant reductions in Hamilton Rating Scale for Depression (Ham-D) scores by study endpoint at 6 weeks, although improvement was noted as early as the first week (Claghorn and Lesem 1995).

A meta-analysis of four randomized, double-blind 6-week studies demonstrated that mirtazapine was as effective as amitriptyline in the treatment of MDD but had significantly fewer adverse anticholinergic, serotonergic, and cardiovascular effects (Stahl *et al.* 1997).

Pooled data from the 6-week U.S. clinical trials that were part of the new drug application showed that approximately 50% of mirtazapine-treated patients and 20% of placebo-treated patients achieved at least a 50% improvement in scores on the Ham-D (Fawcett and Barkin 1998b).

In a randomized, double-blind multicenter study comparing mirtazapine and fluoxetine, both medications were found to be well tolerated in the treatment of MDD, although mirtazapine was noted to demonstrate a significantly greater improvement in Ham-D scores beginning in the third week of treatment (Wheatley *et al.* 1998).

When mirtazapine was compared with paroxetine in a randomized, double-blind study of 275 patients with MDD, the two drugs were found to be equally well tolerated and efficacious overall, but mirtazapine-treated patients had significantly lower Ham-D and Hamilton Anxiety Scale scores at week 1, which possibly suggests a faster onset of therapeutic benefit from mirtazapine (Benkert *et al.* 2000).

Similarly, when compared with citalopram in an 8-week randomized, double-blind multicenter study of 270 patients with MDD, mirtazapine was equally well tolerated and efficacious at study endpoint but was significantly more effective (as assessed by the Hamilton Anxiety Scale, Montgomery-Asberg Depression Rating Scale, and Clinical Global Impression [CGI] Scale scores) at week 2 (Leinonen *et al.* 1999).

It is interesting that in an 8-week randomized, double-blind multicenter study comparing two antidepressants with both serotonergic and noradrenergic activity, mirtazapine was found to be equal in efficacy to venlafaxine in the treatment of MDD

with melancholic features, although it demonstrated a trend (not statistically significant) toward a higher percentage of responders and remitters (Guelfi *et al.* 2001).

In a meta-analysis of 15 studies comparing mirtazapine with an SSRI, Thase *et al.* (2010) concluded that mirtazapine was significantly more likely than the SSRI to induce remission at weeks 1, 2, 4, and 6. At week 2, the remission rates with mirtazapine were more than 70% higher than those with the SSRI, which suggests more rapid effects. A more recent systematic review of a Cochrane database showed that the optimal dosage of mirtazapine appears to be 30 mg/day or less (Furukawa *et al.* 2019).

A study that investigated several combinations of antidepressants versus monotherapy found that mirtazapine coadministered with fluoxetine was significantly more effective than fluoxetine alone. Similarly high rates of remission were observed for mirtazapine coadministered with bupropion and mirtazapine coadministered with venlafaxine (Blier *et al.* 2010).

In contrast to the findings of the Blier *et al.* (2010) study, the National Institute of Mental Health-funded Combining Medications to Enhance Depression Outcomes (CO-MED) study--in which remission and response rates for two antidepressant combinations (escitalopram plus bupropion sustained release and venlafaxine plus mirtazapine) administered from treatment initiation were compared with those for antidepressant monotherapy (escitalopram plus placebo)--failed to detect differences between groups (Rush *et al.* 2011). Baseline insomnia was not a predictor of response to single versus combination antidepressants (Sung *et al.* 2015).

The sleep effects of mirtazapine in MDD were reported by Schmid *et al.* (2006). Mirtazapine improved sleep continuity by day 2 of therapy, and the effect was sustained for at least 4 weeks. At day 28, significant increases in slow-wave and low-delta sleep were also observed.

An 8-week open-label trial of mirtazapine in 22 menopausal patients receiving estrogen replacement therapy who had MDD demonstrated an almost 90% remission rate among the study completers (Joffe *et al.* 2001).

Insufficient Response to Selective Serotonin Reuptake Inhibitor Treatment (Augmentation or Substitution Therapy)

In an 8-week open-label study of 103 outpatients with DSM-IV (American Psychiatric Association 1994) MDD complicated by a lack of response to (or intolerance of) treatment with fluoxetine, paroxetine, or sertraline, approximately one-half of the outpatients demonstrated a 50% reduction in the 17-item Ham-D score when switched to treatment with mirtazapine (Fava *et al.* 2001).

In a 4-week study of patients with persistent MDD despite adequate antidepressant monotherapy, augmentation with mirtazapine resulted in a 45% remission rate compared with a 13% remission rate among patients receiving placebo (Carpenter *et al.* 2002). Of note, in this study there were no significant differences in side effects between drug and placebo (Carpenter *et al.* 2002).

In level 3 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, mirtazapine was compared with nortriptyline in patients whose symptoms had not responded to two previous consecutive antidepressant trials (Fava *et al.* 2006). Level 1 of STAR*D used citalopram; level 2 used a switch to another drug or augmentation.

Nortriptyline produced higher remission rates than did mirtazapine (19.8% vs. 12.3%); however, the difference was not statistically significant.

Depression and Sexual Dysfunction

In an open-label study of 103 patients with depression treated with mirtazapine, 54% of patients who had reported poor or very poor sexual functioning during prior treatment with an SSRI described an improvement in sexual functioning by study endpoint (Fava *et al.* 2001).

Similarly, Gelenberg *et al.* (2000) reported that 58% of patients with prior SSRI-induced sexual dysfunction had a return of normal sexual functioning when they switched to treatment with mirtazapine.

In contrast, augmentation with mirtazapine was no more effective than placebo augmentation in reversing SSRI-associated sexual side effects in patients with fluoxetine-associated sexual dysfunction (Michelson *et al.* 2002).

Depression in Elderly Patients

In a 6-week study of 150 outpatients (ages 55-80 years) with moderate to severe depression, mirtazapine was found to be effective and well tolerated (Halikas 1995). Half of the mirtazapine-treated patients and 35% of the placebo-treated patients demonstrated at least a 50% reduction in Ham-D scores (Halikas 1995). In another study, mirtazapine was significantly more effective than paroxetine at weeks 1, 2, 3, and 6, but not at week 8, in subjects older than 65 years (Schatzberg *et al.* 2002). Differences were observed primarily on measures of anxiety and sleep. A person's status as a carrier of the allele producing the e4 type of apolipoprotein E predicted a positive response to mirtazapine (Murphy *et al.* 2003a).

The oral disintegrating tablet formulation of mirtazapine has been studied in elderly patients and appears to be well tolerated (Nelson *et al.* 2007; Varia *et al.* 2007).

Comorbid or Primary Symptoms of Anxiety

Meta-analyses of placebo-controlled studies of patients with depression and associated symptoms of anxiety have demonstrated that mirtazapine-treated patients exhibit significantly greater improvement in symptoms of anxiety compared with placebo-treated patients (Fawcett and Barkin 1998a; Nutt 1998) beginning as early as the first week of treatment (Fawcett and Barkin 1998a).

Social Anxiety Disorder

Mirtazapine was compared with placebo in a 10-week double-blind comparison study of 66 women with DSM-IV social phobia (changed in DSM-5 [American Psychiatric Association 2013] to *social anxiety disorder*). Mirtazapine appeared to separate from placebo on several primary measures of social anxiety symptoms (Muehlbacher *et al.* 2005).

Generalized Anxiety Disorder

A reanalysis of a primary care MDD randomized controlled trial indicated that comorbid generalized anxiety disorder in MDD was a predictor of a significantly greater response to mirtazapine compared with placebo (Rifkin-Zybutz *et al.* 2020).

Obsessive-Compulsive Disorder

Koran *et al.* (2005) reported on a two-phase study (a 12-week open-label phase followed by an 8-week double-blind discontinuation phase) of mirtazapine (maximum dosage 60 mg/day) in 30 patients with OCD. In the 8-week discontinuation phase, mirtazapine was significantly more effective than placebo in preventing symptom recurrence.

Mirtazapine augmentation of citalopram was assessed in 49 nondepressed patients with OCD (Pallanti *et al.* 2004). Subjects were treated with citalopram plus placebo or citalopram plus mirtazapine under single-blind conditions. Mirtazapine appeared to speed the response to citalopram but not to improve overall response.

Posttraumatic Stress Disorder

In an early 8-week open-label study of six patients with severe chronic PTSD, one-half of the mirtazapine-treated patients demonstrated at least a 50% reduction in the CGI score and significant reductions on scales of PTSD severity (Connor *et al.* 1999).

In a later 6-week double-blind comparison study, mirtazapine was compared with sertraline in Korean veterans (Chung *et al.* 2004). At study endpoint, mirtazapine was statistically significantly superior to sertraline on several measures. Efficacy was apparently maintained to 24 weeks (Kim *et al.* 2005). However, in a more recent study of PTSD among U.S. veterans, mirtazapine failed to separate from placebo (Davis *et al.* 2020).

Alcohol Use Disorder

Mirtazapine was not found to be significantly superior to placebo in reducing alcohol use in a study of men with high alcohol consumption (de Bejczy and Soderpalm 2015), although there was a suggestion that the drug might be helpful in individuals with a family history of alcohol use disorder.

Sleep Disorders

Because of its sedating properties when used to treat depression, mirtazapine has been studied in patients with breathing-related sleep disorders. In a double-blind crossover study of seven patients with obstructive sleep apnea, mirtazapine at dosages of 4.5 mg/day and 15 mg/day produced significantly greater reductions (on the order of 46%-52%) in apnea-hypopnea index scores in comparison with placebo (Carley *et al.* 2007). However, because of concerns regarding weight gain and daytime sedation, the authors concluded that mirtazapine could not at present be recommended as a primary therapy for this disorder. In contrast, Karsten *et al.* (2017) reported that mirtazapine at 7.5 mg/day was significantly more effective than placebo in treating transient insomnia.

Chronic or Recurrent Pain

A number of case reports have indicated that mirtazapine could be beneficial for treating chronic or recurrent pain (Brannon and Stone 1999;

Brannon *et al.* 2000; Kuiken *et al.* 2005; Nutt and Law 1999). In a large observational study conducted in Germany (Freynhagen *et al.* 2006) that involved 600 individuals with comorbid pain and depression treated with mirtazapine, the drug appeared to reduce pain effectively, with a relatively low-order risk of side effects (7%), at a mean dosage of 35 mg/day. The drug has been explored in fibromyalgia with inconclusive results (Ottman *et al.* 2018; Welsch *et al.* 2018).

Mirtazapine 15-30 mg/day was reported to be effective in a double-blind crossover study of 24 nondepressed patients with chronic tension headaches (Bendtsen and Jensen 2004). The area under the curve (intensity x duration) for headache was significantly lower for mirtazapine than for placebo.

Nausea

In a case series of 20 patients with breast or gynecological cancer who were treated with mirtazapine, 19 of the patients demonstrated a significant reduction in symptoms of depression, anxiety, nausea, anorexia, and insomnia. In addition, there were no adverse drug interactions with oncology treatment regimens, including chemotherapy (Thompson 2000).

A 7-week open-label crossover investigation of mirtazapine in 20 patients with cancer found significant improvements in mood, anxiety, insomnia, appetite, weight, and pain symptoms by study endpoint (Theobald *et al.* 2002).

It has been suggested that mirtazapine could prove to be a safe and effective adjunct to cancer chemotherapy because of its ability to treat nausea via a 5-HT$_3$ receptor antagonism effect; insomnia, anorexia, and weight loss via histamine$_1$ receptor antagonism; symptoms of depression via enhanced 5-HT and noradrenergic transmission by way of a$_2$, 5-HT$_2$, and 5-HT$_3$ receptor blockade; and symptoms of anxiety via 5-HT$_2$ and 5-HT$_3$ receptor antagonism (Kast 2001). A randomized, double-blind trial reported that the incidence of nausea and vomiting after spinal anesthesia with intrathecal morphine was significantly lower in orthopedic surgery patients who received preoperative mirtazapine (30 mg) than in those who received placebo (Chang *et al.* 2010).

A review of seven cases of pregnant patients with treatment-refractory hyperemesis gravidarum and symptoms of depression and anxiety concluded that treatment with mirtazapine produced resolution of symptoms without adverse effects on the newborns (Saks 2001).

Vasomotor Symptoms

Waldinger *et al.* (2000) described four cases in which women (ages 39-60 years) experienced a near-complete resolution of symptoms of hot flushes and perspiration within the first week of treatment with mirtazapine.

Respiratory Symptoms

Mirtazapine was reported to not separate from placebo in reducing breathlessness in patients with advanced lung disease (Higginson *et al.* 2020).

Pediatric Depression and Anxiety

Mirtazapine has been assessed in several trials involving children or adolescents with MDD or anxiety disorders. In one trial in 24 adolescents with MDD, patients responded well to mirtazapine, with no dropouts due to side effects (Haapasalo-Pesu *et al.* 2004). In another small open-label trial in 18 patients with DSM-IV social phobia (social anxiety disorder), mirtazapine also demonstrated efficacy (Mrakotsky *et al.* 2008). Although there was a very high dropout rate, most of the discontinuations were not due to side effects.

Pervasive Developmental Disorders

In an open-label study of the use of mirtazapine in 26 patients with DSM-IV pervasive developmental disorders, 35% of subjects demonstrated significant improvement on CGI scores with respect to symptoms of aggression, self-injury, irritability, hyperactivity, anxiety, depression, and insomnia (Posey *et al.* 2001).

Depression in Alzheimer's Disease

Raji and Brady (2001) described three cases of patients with comorbid Alzheimer's dementia (Mini-Mental State Examination scores of 21/30, 11/30, and 18/30) and depressive symptomatology (including weight loss, insomnia, and anxiety) who were treated safely with mirtazapine. The patients demonstrated significant improvements in appetite, weight, sleep, mood, and energy level.

However, in a large-scale trial comparing sertraline (up to 150 mg/day), mirtazapine (up to 45 mg/day), and placebo in Alzheimer's disease patients with depression, there were no differences among the three groups in terms of a reduction in depressive symptoms (Banerjee *et al.* 2011). Given these negative findings regarding benefit and the heightened risk of side effects from these drugs, the authors recommended that the current practice of prescribing antidepressants in this patient population be reconsidered. A more recent approach has been to subtype the depressive symptoms in dementia, and there is a suggestion of a possible subtype that could be helped (Zuidersma *et al.* 2019).

Negative Symptoms in Schizophrenia (Add-On Therapy)

The utility of mirtazapine in the treatment of negative symptoms (i.e., blunted affect, alogia, avolition, asociality, and anhedonia) in schizophrenia has been examined in several studies. In a 6-week double-blind, randomized, placebo-controlled trial, the addition of mirtazapine to haloperidol in the treatment of schizophrenia produced statistically significant reductions in Positive and Negative Syndrome Scale scores as well as in CGI-Severity and CGI-Improvement scores (Berk *et al.* 2001). In addition, Positive and Negative Syndrome Scale negative symptom scores in this study were found to be reduced by 42% in the group of patients who received adjunctive mirtazapine compared with the group who received placebo (Berk *et al.* 2001). Furthermore, the improvement in negative symptoms was not correlated with Ham-D scores at study endpoint, which suggests that the effect of mirtazapine on diminution of negative symptoms in schizophrenia was not a result of improvement in mood symptoms (Berk *et al.* 2001).

In a subsequent study, Berk *et al.* (2009) compared mirtazapine (30 mg/day) with placebo add-on in patients with schizophrenia being treated with atypical antipsychotics. The effects of mirtazapine on negative symptoms and cognition failed to separate from those of placebo.

Several positive studies have followed the mixed findings of Berk and colleagues. Abbasi *et al.* (2010) reported that mirtazapine add-on at 30 mg/day was significantly more effective than placebo in reducing negative symptoms and total Positive and Negative Syndrome Scale scores in patients with schizophrenia being treated with risperidone. Similarly, Cho *et al.* (2011) noted that mirtazapine augmentation separated from placebo in improving negative symptoms and cognition in patients undergoing treatment with risperidone. Neuropsychological testing results likewise showed significantly greater improvement with mirtazapine. Stenberg *et al.* (2010) reported that patients who were not sufficiently improved on first-generation antipsychotics showed significantly greater improvement in cognition with add-on mirtazapine than with placebo.

A meta-analysis examining the safety and efficacy of adjunctive antidepressants for cognitive impairment in schizophrenia included four studies of mirtazapine. In this investigation, statistically significant but minimal clinical effects were noted for all drugs (Vernon *et al.* 2014).

Antipsychotic-Induced Akathisia

Poyurovsky *et al.* (2003, 2006) conducted two double-blind, placebo-controlled studies of mirtazapine treatment of antipsychotic-induced akathisia in patients with schizophrenia. In the first study (Poyurovsky *et al.* 2003), mirtazapine 15 mg/day was compared with placebo in 26 patients. The drug was significantly superior to placebo. In the second study (Poyurovsky *et al.* 2006), mirtazapine 15 mg/day was compared with propranolol 80 mg/day or placebo in 90 patients. Both drugs separated from placebo, but propranolol was associated with clinically significant bradycardia and hypotension.

Side Effects and Toxicology

In a double-blind, placebo-controlled study of outpatients with depression, the most commonly reported side effects associated with mirtazapine treatment were somnolence, increased appetite, and weight gain (Claghorn and Lesem 1995).

In a review of data from the clinical development program for mirtazapine, the only adverse effects that occurred at a higher incidence with mirtazapine versus placebo were excessive sedation, increased appetite, weight gain, and dry mouth (Montgomery 1995). The authors noted that these side effects were typically mild and transient in nature and that they diminished over time even when dosages were increased (Montgomery 1995).

Side effects typical of SSRIs, such as nausea, diarrhea, and sexual dysfunction, appear to occur less frequently in patients treated with mirtazapine (Boyarsky *et al.* 1999; Farah 1998; Montgomery 1995; Stimmel *et al.* 1997).

Mirtazapine appears to be well tolerated in elderly individuals. The side effects most commonly reported--including somnolence, increased appetite, weight gain, and dry mouth--are of the same type as those reported in younger adults (Fawcett and Barkin 1998b; Halikas 1995). In a large study of 170,000 psychiatric inpatients in German-speaking countries (Spindelegger *et al.* 2014), mirtazapine was found to be associated with significantly fewer cardiovascular adverse events compared with all other antidepressants (i.e., monoamine oxidase inhibitors, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and SSRIs).

Mirtazapine appears to have a very low propensity to cause clinically relevant laboratory abnormalities, such as transient elevations in liver enzymes (which occur in about 2% of patients) and severe neutropenia (in

0.1% [Claghorn and Lesem 1995; Fawcett and Barkin 1998b; Kent 2000; Montgomery 1995]). Mirtazapine can significantly reduce cortisol levels in both plasma and saliva. In addition, mirtazapine use is associated with increased plasma concentrations of triglycerides and cholesterol (Laakmann *et al.* 1999, 2003; Merck and Co. 2020).

Mirtazapine appears to have no clinically significant effects on seizure threshold or on the cardiovascular system (Claghorn and Lesem 1995; Fawcett and Barkin 1998b; Kent 2000; Montgomery 1995).

Notably, the noradrenergic effects of mirtazapine appear to be dose dependent and increase significantly at dosages > 15 mg/day. Consistent with this pattern, the sedation associated with mirtazapine's affinity for histamine$_1$ receptors and typically experienced at dosages of [?] 15 mg/day may be counteracted by enhancement of noradrenergic neurotransmission via increased dosages of [?] 30 mg/day (Claghorn and Lesem 1995; Kent 2000). It is likewise hypothesized that the risk of weight gain with mirtazapine is diminished at dosages [?] 30 mg/day (Barkin *et al.* 2000; Fawcett and Barkin 1998b). However, a more recent meta-analysis indicated that mirtazapine was associated with considerable weight gain (average of 1.5 kg) in randomized clinical trials (Domecq *et al.* 2015), and product labeling indicates that weight gain of greater than 7% of body weight has been observed (Merck and Co. 2020).

Use During Pregnancy and Lactation

A study conducted across six countries (Djulus *et al.* 2006) assessed the risk associated with exposure to mirtazapine during pregnancy. Birth outcomes were examined for three groups: pregnant women taking mirtazapine, disease-matched pregnant women taking other antidepressants, and pregnant women exposed to nonteratogens. There were approximately 100 patients per group. The rate of spontaneous abortions in the mirtazapine group (19%) was similar to that in the other antidepressant group (17%) and in the nonteratogen control group (11%). The rate of prematurity was significantly higher in the mirtazapine group (10%) than in the nonteratogen group (2%). The rate of prematurity in the group taking other antidepressants was 7%. The rate of major malformations was not elevated in the mirtazapine group.

In a study of eight women taking mirtazapine while breastfeeding, concentrations of mirtazapine or desmethylmirtazapine were measured in milk and plasma (Kristensen *et al.* 2007). Low infant doses were observed, which led the authors to conclude that the drug is safe for lactating women who breastfeed.

Overdose

Mirtazapine appears to be safe in overdose. In one report (Holzbach *et al.* 1998), the cases of two patients who had overdosed with 30-50 times the average daily dose of mirtazapine were presented. In each case, the patient recovered fully and without any complications.

Symptoms reported in cases of mirtazapine overdose include disorientation, drowsiness, impaired memory, and tachycardia (Fawcett and Barkin 1998b; Kent 2000; Montgomery 1995; Stimmel *et al.* 1997).

A review of 117 mirtazapine overdoses (average ingestion of 450 mg) in Scotland revealed the adverse consequences to be relatively mild (Waring *et al.* 2007). Decreased consciousness was seen in 27% of subjects; 30% demonstrated tachycardia.

A more recent study of overdoses seen at six general hospitals in the United Kingdom between 2000 and 2006 indicated that mirtazapine was of intermediate toxicity between tricyclic antidepressants and venlafaxine on the one hand and SSRIs on the other (Hawton *et al.* 2010). Another study of 239,000 patients in the United Kingdom reported that mirtazapine was significantly more likely than citalopram to be associated with suicide, attempted suicide, or self-harm; however, the number of events was low (Coupland *et al.* 2015). Trazodone and venlafaxine were also associated with more overdose events. That mirtazapine and trazodone--two sedating antidepressants often prescribed for depressed patients with comorbid sleep problems--were both noted to be associated with suicidal behavior raises the possibility that baseline insomnia, rather than specific drug effects, might explain at least some of the increased risk of suicide attempts.

Drug-Drug Interactions

In vitro data suggest that mirtazapine is unlikely to have clinically significant effects on the metabolism of drugs by CYP enzymes (Barkin *et al.* 2000; Fawcett and Barkin 1998b; Kent 2000). Analyses of data from the clinical development program for mirtazapine and post-marketing surveillance reveal no clinically relevant drug-drug interactions from the concomitant use of medications such as opiates, anticonvulsants, analgesics, antihypertensives, diuretics, or nonsteroidal anti-inflammatory drugs (Barkin *et al.* 2000; Fawcett and Barkin 1998b). However, few formal drug interaction studies involving mirtazapine have been conducted (Barkin *et al.* 2000; Fawcett and Barkin 1998b; Holm and Markham 1999). Of note, a study of elderly patients with depression allowed patients to take drugs that were CYP2D6 substrates (Schatzberg *et al.* 2002). In this study, no increase in side effects was observed in these patients compared with patients who were not taking CYP2D6 substrate agents (Schatzberg *et al.* 2002). Because somnolence is a recognized side effect of mirtazapine, excessive sedation may occur when it is used with other agents known to cause CNS depression (e.g, benzodiazepines, antihistamines, ethanol, cannabinoids).

Conclusion

Mirtazapine is derived from the piperazinoazepine class of compounds and thus is structurally unrelated to any other psychotropic medication. Mirtazapine is also unique as an antidepressant because of its 5-HT$_2$, 5-HT$_3$, and a$_2$ receptor antagonist pharmacodynamic profile, which results in enhancement of noradrenergic and serotonergic transmission. It is an antidepressant that has been shown to be efficacious and well tolerated in the treatment of depression, and there are indications that it may be effective in treating a number of other medical and psychiatric conditions. Moreover, mirtazapine may offer a more rapid amelioration of symptoms of depression and anxiety compared with other antidepressants. The most common side effects reported with mirtazapine are somnolence, increased appetite, weight gain, and dry mouth. It otherwise appears to be free of many of the adverse effects typical of SSRIs, especially sexual dysfunction.

Furthermore, mirtazapine appears to be well tolerated and effective in the treatment of geriatric depression and to have benefit as an add-on agent in treating schizophrenia. In addition, mirtazapine is considered to be relatively safe in overdose, with case reports documenting complete and uncomplicated recovery following ingestion of up to 50 times the average daily dose. Finally, mirtazapine appears to be devoid of clinically significant drug-drug interactions, although larger formal clinical trials are still needed to verify this.

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CHAPTER 18

Bupropion

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History and Discovery

Bupropion was discovered when investigators were searching for an antidepressant with a novel mechanism of action and safer side-effect profile compared with the antidepressants available at that time. Synthesized in 1966, this unique compound, unlike tricyclic antidepressants and monoamine oxidase inhibitors, was found to have antidepressant activity in animal models that are predictive of antidepressant activity in humans (Soroko and Maxwell 1983). Bupropion's tolerability profile is superior to that of selective serotonin reuptake inhibitors (SSRIs), with less weight gain, less sedation, no withdrawal symptoms upon discontinuation, and minimal sexual side effects (Thase *et al.* 2005).

Bupropion first received FDA approval in 1985 and was on the brink of release when a study by Horne *et al.* (1988) reported that 4 of 55 inpatients with bulimia experienced seizures during treatment with the medication. Further research revealed that the risk of seizures increased with dosage, from a risk of 0.3%-0.4% at a dosage of 450 mg/day to a risk of almost 2% at a dosage of 600 mg/day. Bupropion was reintroduced in 1989 with a maximum recommended dosage of 450 mg/day (Davidson 1989). The original immediate-release formulation of bupropion was dosed three times daily (GlaxoSmithKline n.d.). In an effort to improve tolerability and safety, a sustained-release (SR) formulation of bupropion, dosed twice daily, was subsequently introduced (GlaxoSmithKline n.d.), and a once-daily extended-release (XL) formulation became available in 2003 (Bausch Health Companies 2021). Care must be taken to differentiate the XL product from the SR product when prescribing. Bupropion is available in two salt forms. Bupropion hydrochloride 150 mg is approximately equivalent to 174 mg of bupropion hydrobromide. A bupropion hydrochloride/naltrexone hydrochloride combination product is also marketed for the treatment of obesity (Currax Pharmaceuticals 2021; see subsection "Obesity" later in chapter).

Structure-Activity Relations

Bupropion, 2-(tert-butylamino)-1-(3'-chlorophenyl)propan-1-one, is a monocyclic antidepressant and a member of the aminoketone group (Figure 18-1). It was designed as a simple chemical structure that in vivo would result in relatively innocuous metabolites (Mehta 1983). Chemically speaking, bupropion is an organic base with a high degree of both water and lipid solubility, which results in good systemic absorption. Its relatively benign side-effect profile is due to the absence of heterocyclic rings as well as other common functional groups (Mehta 1983).

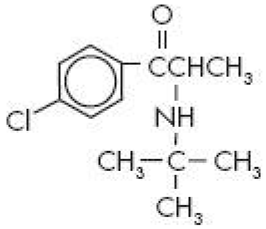

FIGURE 18-1. Chemical structure of bupropion.

It has been noted that bupropion shares some structural and neurochemical properties with sympathomimetics and has a phenylethylamine skeleton similar to that of amphetamine. As may be expected from this structural similarity, a study of false-positive amphetamine urine drug screens found therapeutic use of bupropion to be the most common cause (Casey *et al.* 2011). Despite the similarity, an early study by Griffith *et al.* (1983) comparing the effects of bupropion and amphetamine in individuals with a history of amphetamine abuse concluded that bupropion had little potential for abuse in humans. However, reports have described cases in which bupropion was perceived as a psychostimulant by patients with a previous history of cocaine abuse (Vento *et al.* 2013). Bupropion is also valued as a stimulant of abuse in the incarcerated population (Hilliard *et al.* 2013). This highlights the need to monitor bupropion users for potential abuse, especially those patients with a history of stimulant use disorders.

Pharmacological Profile

Bupropion inhibits the reuptake of dopamine and norepinephrine by acting as a nonselective inhibitor of the dopamine transporter (DAT) and the norepinephrine transporter (NET). Studies show that bupropion also acts as an antagonist to nicotinic acetylcholine receptors. Preclinical data indicate that bupropion does not bind to postsynaptic histamine, a- or b-adrenergic, or serotonin receptors, nor does it inhibit monoamine oxidase (Ascher *et al.* 1995; Baldessarini 2001; Fava *et al.* 2005; Stahl *et al.* 2004). Thus, of the myriad antidepressants now available, bupropion is the only agent without substantial serotonergic activity (Ascher *et al.* 1995; Richelson 1996; Stahl *et al.* 2004). Bupropion's lack of action at histamine and serotonin receptors confers a favorable side-effect profile, including an absence of weight gain, somnolence, and sexual side effects (Settle *et al.* 1999).

Pharmacokinetics and Disposition

Bupropion is rapidly absorbed in the gastrointestinal tract after oral administration (Findlay *et al.* 1981; Jefferson *et al.* 2005). Absorption has been found to be close to 100% (Schroeder 1983). After first-pass metabolism, systemic bioavailability of the drug is decreased. Peak plasma levels occur within 2 hours, 3 hours, and 5 hours for the immediate-release, SR, and XL formulations, respectively (Jefferson *et al.* 2005; Schroeder 1983). Food does not impair absorption, so doses may be administered without regard to meal times. Protein binding ranges from 82% to 88%, which is not high enough to be of clinical importance (Jefferson *et al.* 2005). The elimination half-life for bupropion is 21 (+- 9) hours, and the half-life for hydroxybupropion, the major metabolite of bupropion, is close to 20 (+- 5) hours (Clayton 2007; Jefferson *et al.* 2005). Steady state occurs in 7-10 days. Finally, excretion in the urine occurs with 0.5% of the drug unchanged (Findlay *et al.* 1981; Jefferson *et al.* 2005).

Bupropion is metabolized extensively by the liver. The major metabolite, hydroxybupropion, is hydrolyzed by cytochrome P450 (CYP) 2B6 (Hesse *et al.* 2000; Kirchheiner *et al.* 2003). Whereas CYP2B6 is the primary isoenzyme involved in bupropion's metabolism, other isoforms, including 1A2, 2A6, 2CP, 2D6, 2E1, and 3A4, also play a small role (Hesse *et al.* 2000; Kirchheiner *et al.* 2003).

In examinations of the pharmacokinetics of bupropion in regard to gender, age, and smoking status, no significant effect has been found, and definitive results have been inconclusive (Daviss *et al.* 2006; Hsyu *et al.* 1997; Jefferson *et al.* 2005). One study in elderly patients found evidence for an extended half-life of bupropion and for the accumulation of metabolites (Sweet *et al.* 1995). Because levels of bupropion and its metabolites have been found to be increased in populations with impaired renal and/or hepatic function relative to healthy control subjects (DeVane *et al.* 1990; Jefferson *et al.* 2005; Worrall *et al.* 2004), dosing should be initiated at lower levels in these patients. The manufacturer has recommended that bupropion be used with caution in patients with mild to moderate liver disease and with extreme caution in patients with severe liver disease (GlaxoSmithKline n.d.).

Mechanism of Action

Bupropion inhibits the reuptake of dopamine and norepinephrine by acting as a nonselective inhibitor of the DAT and the NET. Two of its active metabolites--hydroxybupropion and threohydrobupropion--have also been shown in in vitro studies to inhibit both the NET and the DAT (Ascher *et al.* 1995).

Whereas other antidepressants that affect NET receptors are thought to produce their effects by downregulating postsynaptic noradrenergic receptors, bupropion differs in that it decreases the firing rate of neurons in the locus coeruleus in a dose-dependent manner (B. R. Cooper *et al.* 1994; T. B. Cooper *et al.* 1984). Acute administration of bupropion not only decreases the firing of brain stem norepinephrine and dopamine neurons but also increases extracellular norepinephrine and dopamine concentrations in the nucleus accumbens (Fava *et al.* 2005). Furthermore, the efficacy of bupropion and hydroxybupropion has been shown to diminish in animal models when norepinephrine-or dopamine-blocking drugs are administered (Cooper *et al.* 1980; Dwoskin *et al.* 2006).

Studies have demonstrated that bupropion raises dopamine concentrations by causing a rapid and reversible increase in vesicular dopamine reuptake via cellular redistribution of the vesicular monoamine transporter 2 protein. By increasing the presynaptic pool of dopamine available for release, it further augments the concentration of dopamine in the extracellular space, which adds to the therapeutic efficacy of this compound (Dwoskin *et al.* 2006; Rau *et al.* 2005).

Outside of its action on the DAT and the NET, bupropion has been shown to work by noncompetitive inhibition of nicotinic acetylcholine receptors (Dwoskin *et al.* 2006). This action may partially contribute to bupropion's efficacy not only as an antidepressant but also as an agent to facilitate tobacco cessation.

Indications and Efficacy

Primary Indications

Major Depressive Disorder

Bupropion's efficacy in the treatment of major depressive disorder (MDD) is supported by many clinical trials. The drug's three formulations are equally useful for this therapeutic indication (Fabre *et al.* 1983; Lineberry *et al.* 1990). Comparison trials have demonstrated that bupropion is as effective as other classes of antidepressants, including tricyclic antidepressants and SSRIs (Branconnier *et al.* 1983; Clayton *et al.* 2006; Coleman *et al.* 1999, 2001; Croft *et al.* 1999; Feighner *et al.* 1986; Kavoussi *et al.* 1997; Mendels *et al.* 1983; Thase *et al.* 2005; Weihs *et al.* 2000).

The development of bupropion SR launched several comparison studies with SSRIs, all of which demonstrated that bupropion's effectiveness in treating symptoms of depression was equal to that of SSRIs. In most studies, the effective daily dose of bupropion SR was between 300 mg and 400 mg (Coleman *et al.* 1999, 2001; Croft *et al.* 1999; Kavoussi *et al.* 1997; Weihs *et al.* 2000). In a meta-analysis of remission data from all available studies comparing bupropion SR and an SSRI, Thase *et al.* (2005) found that remission rates were essentially the same for the two types of antidepressants. Bupropion SR has also been shown to prevent relapse of depressive symptoms in continuation treatment extending up to 1 year (Weihs *et al.* 2002).

The release of bupropion XL in 2003 also generated several comparison studies. In two 8-week placebo-controlled comparison trials of bupropion XL and escitalopram, pooled analysis confirmed equivalent efficacy of the two agents based on the mean change in Hamilton Rating Scale for Depression (Hamilton 1960) scores (Clayton *et al.* 2006). Similarly, in a double-blind comparison trial of bupropion XL (300-450 mg/day) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine XR (150-225 mg/day), both agents produced similar mean changes in Hamilton Rating Scale for Depression scores, although remission rates were significantly higher with bupropion (Thase *et al.* 2006).

Studies have shown bupropion to be efficacious in the treatment of MDD, not only as monotherapy but also as an augmenting agent with SSRIs or SNRIs (Bodkin *et al.* 1997; DeBattista *et al.* 2003; Fava *et al.* 2003; Ferguson *et al.* 1994; Lam *et al.* 2004; Rush *et al.* 2006; Spier 1998; Stern *et al.* 1983; Trivedi *et al.* 2006). Although the "triple monoamine approach" (i.e., using an SSRI with bupropion to block reuptake of serotonin, dopamine, and norepinephrine) is often a useful strategy, Stewart *et al.* (2014) demonstrated that the addition of bupropion XL at a relatively high dosage (i.e., 450 mg/day) to a similarly high dosage of escitalopram (i.e., 40 mg/day) increased neither the speed of recovery nor the likelihood of recovery from a major depressive episode. Nasr *et al.* (2014) compared the outcomes of patients who received either aripiprazole or bupropion as an adjunct to SSRI treatment. Although no overall differences were found between the two augmenting agents, bupropion was significantly more helpful in treating poor energy and motivation, whereas aripiprazole proved superior in reducing suicidal ideation. This finding suggests that a careful symptom inventory is the best guide in selecting an augmenting agent.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was the largest protocol-driven study of MDD ever undertaken, with an initial study population of 4,041. A retrospective analysis of this study directly addressed the question of which next-step strategy--medication augmentation or medication switching--yields the best outcome for patients whose symptoms have not improved after an adequate trial of antidepressant monotherapy (Gaynes *et al.* 2012). Findings specific to bupropion suggested that patients who completed an initial 12-week period of citalopram treatment without experiencing complete symptom remission received more benefit from augmenting citalopram with bupropion than from discontinuing citalopram and switching to bupropion.

In August 2022, the FDA approved dextromethorphan-bupropion hydrochloride extended-release tablets for the treatment of MDD in adults (Axsome Therapeutics 2022). Dextromethorphan (DXM) is an *N*-methyl-D-aspartate (NMDA) receptor antagonist with additional effects at serotonin transporters and NETs and nicotinic and sigma-1 receptors (Majeed *et al.* 2021). In an industry-sponsored (Axsome Therapeutics) randomized, double-blind trial of DXM/bupropion (AXS-05) versus bupropion alone (105 mg twice daily), O'Gorman *et al.* (2019) reported that at 6 weeks, 47% of patients treated with DXM/bupropion achieved remission, compared with 16% of those treated with bupropion alone. A follow-up Phase III double-blind, placebo-controlled, industry-sponsored trial (O'Gorman *et al.* 2020) found similar results, with DMX/bupropion being associated with statistically significant reductions in total Montgomery-Asberg Depression Rating Scale (Montgomery and Asberg 1979) scores compared with placebo beginning at week 1.

It was hypothesized that the two drugs may produce more rapid relief from depression than bupropion alone by achieving pharmacological synergy through the targeting of multiple monoamines and receptors. Furthermore, therapeutic plasma levels of DXM are achieved through inhibition of its metabolism by bupropion's actions at CYP2D6. Each extended-release tablet contains 45 mg of DXM and 105 mg of bupropion (Axsome Therapeutics 2022). The recommended dosing strategy is one tablet daily for 3 days, after which the dosage can be increased to one tablet twice daily (except in the context of moderate renal impairment or poor metabolism of CYP2D6), with doses separated by at least 8 hours. The most common adverse reactions include dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis (Axsome Therapeutics 2022).

Depression in the elderly. Depression in the elderly is often underdiagnosed and may go untreated. Older individuals tend to describe nonspecific somatic symptoms, such as insomnia, anorexia, and low energy, instead of reporting depressed mood (Birrer and Vemuri 2004). Bupropion has been found to be an effective antidepressant in elderly patients (Birrer and Vemuri 2004; Branconnier *et al.* 1983; Weihs *et al.* 2000). A study comparing bupropion SR and the SSRI paroxetine noted that although both agents were effective in treating depression, bupropion SR had a more favorable side-effect profile (Weihs *et al.* 2000). Like bupropion SR, bupropion XL has shown efficacy in the treatment of depression in elderly individuals (Clayton 2007). However, a study examining whether gender-or age-related differences in efficacy exist between SSRIs and bupropion for the treatment of MDD found SSRIs and bupropion to be equally effective in treating depressive symptoms, anxiety/somatic symptoms, and insomnia across all age and gender groups (Papakostas *et al.* 2007).

Depression with decreased energy, interest, and pleasure. Bupropion XL has been studied specifically in depressed patients with a retarded/anergic symptom profile. Jefferson *et al.* (2006) showed that bupropion XL was more effective than placebo in depressed patients with decreased energy, pleasure, and interest. Bupropion's unique norepinephrine-dopamine reuptake inhibitor mechanism of action may play a role in its effectiveness in treating these symptoms (Jefferson *et al.* 2006).

Depression with anxiety symptoms. Studies have demonstrated the effectiveness of bupropion at dosages of 300-400 mg/day in reducing symptoms of anxiety in patients with MDD (Fabre *et al.* 1983). Moreover, bupropion and SSRIs appear to be equally effective in reducing symptoms of anxiety associated with MDD in both the general population and the elderly (Feighner *et al.* 1991; Weihs *et al.* 2000). In 2001, Trivedi *et al.* published results of a study examining the effects of bupropion SR versus sertraline on anxiety in depressed patients, reporting that both bupropion SR and sertraline were superior to placebo in allaying depressive symptoms; however, the treatment of anxiety symptoms did not significantly differ from placebo for either active medication. The study concluded that bupropion and SSRIs were comparable in their antidepressant and anxiolytic effects in patients with MDD. Neither was favored for more specific management of anxiety (Trivedi *et al.* 2001). A meta-analysis comparing the efficacy of bupropion and SSRIs for the treatment of anxiety symptoms in MDD concluded that both classes of medication led to a similar degree of improvement in anxiety symptoms, with no significant difference in the severity of residual anxiety symptoms (Papakostas *et al.* 2008).

Depression with seasonal pattern (seasonal affective disorder).

In 2006, bupropion XL (Bausch Health Companies 2021) became the first medication to receive a labeled indication for the preventive treatment of seasonal depressive symptoms, and it is still the only medication to have received such an indication. A study published in 1992 initially suggested bupropion's efficacy as a treatment for winter depression (Dilsaver *et al.* 1992). In 2005, Modell *et al.* published the results of three prospective randomized, placebo-controlled prevention trials involving 1,042 outpatients with a diagnosis of seasonal major depressive episodes. Patients received 150-300 mg/day of bupropion XL or placebo in autumn while they were still well. Bupropion XL reduced the frequency of emergence of winter depression by 44% and protected against the recurrence of seasonal major depressive episodes. Furthermore, there was no noticeable increase in major depressive episodes following discontinuation of bupropion in the springtime (Modell *et al.* 2005).

Bipolar depression. A small number of early studies demonstrated the advantages of bupropion in the treatment of depression in bipolar disorder (Haykal and Akiskal 1990; Shopsin 1983; Wright *et al.* 1985). Although these investigations yielded positive results, they were limited by small numbers of subjects and lack of placebo control. Several trials have examined the risk of treatment-emergent mania with adjunctive use of bupropion in bipolar disorder. Although there appears to be a lower risk of mania with bupropion and SSRIs than with the SNRI venlafaxine, findings regarding bupropion's efficacy in treating depressive symptoms in bipolar disorder have been mixed (Leverich *et al.* 2006; Post *et al.* 2006; Sachs *et al.* 2007).

Smoking Cessation

In 1997, bupropion SR received FDA approval for use as a smoking cessation aid under the trade name Zyban (GlaxoSmithKline 2006). The beneficial effect of bupropion on smoking cessation was first noted when researchers observed unplanned suspension of smoking in depressed subjects who were being treated with bupropion (reviewed in Hudziak and

Rettew 2004). In a double-blind placebo-controlled trial of bupropion SR therapy for smoking cessation (Hurt *et al.* 1997), 615 subjects received bupropion SR at dosages of 100 mg/day, 150 mg/day, or 300 mg/day for 7 weeks, with a target quit date of 1 week after beginning treatment. Brief counseling was also provided. Rates of smoking cessation at the end of 7 weeks were 29% for the 100 mg/day group, 39% for the 150 mg/day group, and 44% for the 300 mg/day group versus 10% for placebo. At 1 year, rates for the three bupropion dosage groups were 20%, 23%, and 23%, respectively, compared with 12% for the placebo group.

For smoking cessation, the recommended dosing is 150 mg/day for 3 days, then 150 mg twice daily for 7-12 weeks, with patients setting a quit date of 1-2 weeks after treatment has been initiated. In 2003, Ferry and Johnston published a 5-year review of the accumulated efficacy and safety data for bupropion SR since its 1997 approval for smoking cessation. A benefit-risk analysis assuming a 30% 1-year quit rate concluded that for every 10,000 smokers treated with bupropion SR, 19 lives are saved and 86 cases of smoking-attributed morbidity are avoided, whereas the risk of a serious adverse effect from treatment is 0.22% (Ferry and Johnston 2003). More recent data have confirmed that bupropion evidences no increased risk of self-harm, suicide, or depression compared with either varenicline or nicotine replacement therapy (Thomas *et al.* 2013). Use of nicotine replacement therapy together with bupropion has been reported to improve smoking cessation outcomes (Siu and U.S. Preventive Services Task Force 2015).

Obesity

Unlike other classes of antidepressants, bupropion is well known for its lack of association with weight gain. In fact, mild, acute weight loss has been noted in many clinical trials. To further investigate this observation, Gadde *et al.* (2001) conducted a randomized, placebo-controlled trial investigating the tolerability and efficacy of bupropion (100-400 mg/day) for weight loss in 50 obese women. All subjects kept a food journal and were placed on a 1,600 kcal/day diet. At 8 weeks, subjects receiving bupropion had achieved greater weight loss compared with those on placebo. At 24 weeks, responders to bupropion had lost an average of 13% of their baseline body weight (Gadde *et al.* 2001). Following this initial study of bupropion for weight loss, two larger studies confirmed these results (Anderson *et al.* 2002; Jain *et al.* 2002).

In 2014, the FDA approved Contrave (Currax Pharmaceuticals 2021), a bupropion/naltrexone combination, for the treatment of patients who are obese (defined as BMI [?] 30 kg/m^2) or overweight (defined as BMI [?] 27 kg/m^2) and have at least one cardiovascular risk factor (Apovian *et al.* 2013). FDA approval followed studies showing that bupropion/naltrexone combination therapy led to reductions in total and visceral adiposity (Smith *et al.* 2013). A drug safety evaluation of bupropion/naltrexone concluded that it led to greater weight loss compared with two other medications approved by the FDA for the treatment of obesity, orlistat and lorcaserin, but less weight loss compared with topiramate/phentermine combination therapy (Verpeut and Bello 2014). Furthermore, a study using functional MRI demonstrated decreased reactivity to food cues following a course of bupropion/naltrexone therapy (Wang *et al.* 2014).

Other Uses

ADHD

Currently there is no FDA indication for bupropion's use in treating ADHD, although studies have demonstrated that it may be helpful in treating symptoms of ADHD in both children and adults (Conners *et al.* 1996; Simeon *et al.* 1986). Clinical trials in children with ADHD have shown bupropion to be a safe and effective alternative to stimulants for treating this disorder (Conners *et al.* 1996), with efficacy similar to that of methylphenidate reported in one comparison trial (Barrickman *et al.* 1995). Bupropion has also been studied in adults with ADHD and has demonstrated statistically significant symptom improvement in this population (Wilens *et al.* 2001). In a meta-analysis by Peterson *et al.* (2008), long-acting forms of bupropion appeared to exhibit clinical effectiveness similar to that of long-acting stimulants in adults. An open trial by Riggs *et al.* (1998) suggested that bupropion may also be useful for the treatment of ADHD in adolescents with comorbid conduct disorder and substance use disorders. A large review of meta-analyses (Moriyama *et al.* 2013) concluded that bupropion therapy is more effective than placebo but less effective than stimulant therapy in the treatment of ADHD.

Overall, bupropion may be a reasonable alternative to stimulants for treating patients with ADHD and comorbid substance use disorders when clinicians would like to avoid prescribing controlled substances.

Sexual Dysfunction

Bupropion has been found in numerous studies of patients with MDD (using validated questionnaires) to be significantly less likely than SSRIs or SNRIs to cause sexual dysfunction, which has led to investigations of bupropion as an antidote to SSRI-induced sexual dysfunction. A placebo-controlled comparison trial of bupropion SR treatment in 42 patients with SSRI-induced sexual dysfunction concluded that bupropion SR increased both the desire to engage in sexual activity and the frequency of engaging in sexual activity relative to placebo (Clayton *et al.* 2004). Safarinejad *et al.* (2010) demonstrated bupropion's efficacy in reversing SSRI-induced sexual dysfunction in men.

Segraves *et al.* (2001) found that bupropion may be helpful in the treatment of DSM-IV-TR hypoactive sexual desire disorder (HSDD; American Psychiatric Association 2000). Subsequently, a double-blind placebo-controlled trial supported this finding and also revealed increases in sexual arousal, orgasm completion, and sexual satisfaction in women with DSM-IV-TR HSDD who received bupropion (Segraves *et al.* 2004). Additional studies have also demonstrated that bupropion may be helpful for treating sexual disorders in both men and women (Modell *et al.* 2000). In a review of non-testosterone treatment options available for HSDD, Lodise (2013, p. 411) concluded that "bupropion is the primary pharmacological agent that has shown positive results."

Pending Investigations

AXS-05, the combination DXM/bupropion medication that was approved for MDD in August 2022, is also being investigated for the treatment of agitation in Alzheimer's disease and for smoking cessation (Stahl 2019). The FDA granted this agent a Breakthrough Therapy designation for the treatment of Alzheimer's-related agitation in June 2020 after the Addressing Dementia via Agitation-Centered Evaluation-1 (ADVANCE-1) Phase II trial--which compared DXM/bupropion versus bupropion versus placebo in patients with probable Alzheimer's disease with clinically significant agitation--demonstrated statistically significant reductions in the Cohen Mansfield Agitation Inventory (CMAI) relative to both placebo and bupropion alone at week 5 (Axsome Therapeutics 2020). The subsequent Phase III ADVANCE-2 trial was completed in early 2023 (ClinicalTrials.gov NCT03226522), but results have not yet been published. In the Phase II trial of AXS-05 versus bupropion SR for smoking cessation, AXS-05 met its primary outcome of reduced smoking intensity (as measured by number of cigarettes smoked per day) relative to bupropion alone (ClinicalTrials. gov NCT03471767).

Side Effects and Toxicology

Evidence from thousands of clinical trials and millions of patient exposures confirms that bupropion is a safe and generally well-tolerated medication across populations. Because of bupropion's unique mechanism of action and structure, its reported side effects are somewhat different from those of other antidepressants.

In a series of large randomized, placebo-controlled multicenter trials evaluating the safety of bupropion SR in the treatment of depressed outpatients, Settle *et al.* (1999) found that the most commonly reported adverse effects (occurring in > 5% of subjects) were headache, dry mouth, nausea, insomnia, constipation, and dizziness. Only three of these--dry mouth, nausea, and insomnia--occurred at higher rates in patients taking bupropion SR than in those receiving placebo. The rate of discontinuation due to adverse effects was low: 7% for bupropion SR compared with 4% for placebo. Rash, nausea, agitation, and migraine were the most common adverse effects leading to discontinuation (Settle *et al.* 1999). Other adverse events reported in at least 1% of patients receiving bupropion in clinical trials, with a frequency greater than placebo, are pruritus, excessive sweating, tremor, agitation, and anxiety (GlaxoSmithKline n.d.).

The side-effect profile of bupropion XL is similar to that of the other bupropion formulations and compares favorably with that of other controlled-release antidepressants. Compared with venlafaxine XR, bupropion XL was found to be associated with lower rates of dry mouth, nausea, diarrhea, somnolence, sedation, and yawning (Clayton *et al.* 2006). A review by Fava *et al.* (2005) also concluded that bupropion produces much less somnolence compared with SSRIs. Moreover, insomnia, thought to be a particular side effect of bupropion, in fact occurs at rates similar to those seen with SSRIs (Fava *et al.* 2005).

Bupropion SR treatment has been associated with lower rates of sexual dysfunction in comparison with treatment with SSRIs (Thase *et al.* 2005). Similarly, in a head-to-head trial of bupropion XL and venlafaxine XR, Thase *et al.* (2006) found that venlafaxine XR had adverse effects on sexual function whereas bupropion did not.

Less common but potentially harmful adverse effects associated with bupropion include allergic reactions, seizures, and changes in vital signs. Allergic reactions, including rash, arthralgias, fever, and serum sickness-like reactions, have been reported (McCollom *et al.* 2000; Tripathi and Greenberger 1999). Thus, it is important to evaluate any reports of previous hypersensitivity before prescribing bupropion.

Clinicians should screen for a history of seizure disorder, other organic brain disease, or bulimia nervosa before prescribing bupropion. Seizure has been reported at a rate of 0.1% at dosages up to 300 mg/day with bupropion SR, with a dose-related effect (Dunner *et al.* 1998). This rate is similar to rates observed with other newer antidepressants, such as SSRIs and mirtazapine, but is lower than rates associated with therapeutic dosages of tricyclic antidepressants (Montgomery 2005). The incidence of seizure with bupropion XL has not been reported in the literature.

Although cases of spontaneous hypertension with bupropion therapy have been reported, clinical trials across the approved dosage range have shown minimal changes in heart rate and blood pressure, even among patients previously diagnosed with hypertension (Jorenby *et al.* 1999; Settle *et al.* 1999; Thase *et al.* 2008). In a smoking cessation study, patients receiving combination treatment with bupropion SR and a nicotine patch had a higher incidence of new or worsening hypertension compared with patients receiving either treatment alone or placebo (Jorenby *et al.* 1999). Thase *et al.* (2008) conducted a dose-response study to evaluate the potential of bupropion to elevate blood pressure. Bupropion SR dosages of 150-400 mg/day were administered to 296 nondepressed volunteers with mild hypertension. Findings indicated that bupropion SR did not separate from placebo on blood pressure changes. However, clinicians should be aware that elevated blood pressure is a possibility with bupropion therapy and should monitor patients accordingly.

Many agents used to treat depression have been associated with weight gain. This effect is thought to be associated with affinity for the H_1 histamine receptor, which is not a factor with bupropion. In fact, mild weight loss over time, rather than weight gain, has been reported with bupropion treatment (Harto-Truax *et al.* 1983). Studies have shown bupropion XL to be associated with weight loss of 0.1-1.1 kg in the short term compared with placebo, which was associated with a small gain of 0.1-0.8 kg (Jefferson *et al.* 2006; Modell *et al.* 2005; Thase *et al.* 2006). In a longer term study on

depression relapse prevention, Croft *et al.* (2002) observed that patients with higher BMIs at baseline experienced greater weight loss with bupropion XL than did patients with lower baseline BMIs.

Overall, at approved dosages, bupropion is a safe medication for treating depression in most populations and has an excellent tolerability profile. However, high blood levels of bupropion can be fatal. Serious medical consequences, such as hypertension, acidosis, sinus tachycardia, seizures, cardiotoxicity with QRS widening, and even death, have been reported with overdoses of bupropion (Bhattacharjee *et al.* 2001; Curry *et al.* 2005; Shrier *et al.* 2000).

On initiation of bupropion therapy, it is usually not necessary to obtain routine laboratory evaluations, although cases of elevated serum transaminase (Oslin and Duffy 1993) and rare cases of hepatitis (Hu *et al.* 2000) have been reported.

Overall, data on the use of bupropion in pregnancy suggest that there are no impacts on the rate of congenital abnormalities, low birthweight, or premature birth (Turner *et al.* 2019), although data on any long-term risks of prenatal bupropion exposure are lacking. Bupropion and its metabolites are detectable in breast milk, though surveyed mothers largely report no clinically detectable adverse effects in their infants (Drugs and Lactation Database 2015). Although there are some case reports of seizures possibly related to bupropion in breast milk, a retrospective database study comparing women who took bupropion alone, an SSRI alone, or a combination of bupropion and an SSRI found no seizures in infants exposed to bupropion and one seizure in an infant exposed to an SSRI alone (reviewed in Drugs and Lactation Database 2015). Thus, seizures are likely not a major concern in breastfeeding infants of mothers taking bupropion.

Drug-Drug Interactions

As discussed earlier, the main enzyme responsible for the metabolism of bupropion is CYP2B6. Competitive inhibition of metabolism can occur with other drugs processed by this enzyme, such as paroxetine, sertraline, diazepam, clonazepam, clopidogrel, ritonavir, and efavirenz (Hesse *et al.* 2000; Jefferson *et al.* 2005).

Bupropion and its major metabolite, hydroxybupropion, are also strong inhibitors of CYP2D6, an enzyme that plays a role in the metabolism of several classes of medications, including antidepressants, antipsychotics, b-blockers, and antiarrhythmic agents (Wilkinson 2005). Studies of the effects of bupropion on CYP2D6 activity are limited, but results of those conducted suggest that bupropion may increase blood levels of drugs metabolized by CYP2D6, such as desipramine and venlafaxine (Jefferson *et al.* 2005; Kennedy *et al.* 2002). An 8-week open-label study of bupropion

SR co-administered with venlafaxine, paroxetine, or fluoxetine found inhibition of venlafaxine metabolism and higher concentrations of venlafaxine but no significant interaction effects with paroxetine or fluoxetine (Kennedy *et al.* 2002). Because of the effects of CYP2D6 inhibition, dosages of voritioxetine should be reduced by one-half if bupropion is administered concomitantly (Takeda Pharmaceuticals 2021). Other agents known to induce various metabolic pathways have also been shown to affect the metabolism of bupropion. Carbamazepine, which induces CYP2B6, CYP3A4, and CYP1A2 activity, has been shown to decrease bupropion concentrations but increase hydroxybupropion concentrations (Ketter *et al.* 1995).

Bupropion should be used with caution in combination with other psychotropic agents that can lower the seizure threshold, such as tramadol, certain antidepressants, and antipsychotics (Delanty *et al.* 1998; Gardner *et al.* 2000). It should also be used with caution in people who abuse alcohol, because this population may have a higher risk of seizures (Dunner *et al.* 1998). In addition, because bupropion increases dopamine reuptake, additive effects with other dopaminergic agents (e.g., levodopa) are a possibility (Goetz *et al.* 1984).

Conclusion

Bupropion is unique among antidepressants in that it functions as a dopamine and norepinephrine reuptake inhibitor and as an antagonist of nicotinic acetylcholine receptors. Because bupropion has no measurable serotonergic activity, its side-effect profile differs markedly from those of other antidepressants, and it provides a treatment alternative for individuals who cannot tolerate or who do not respond to SSRIs. Although its current FDA-approved indications are limited to the treatment of MDD, seasonal depressive symptoms, tobacco use disorder, and obesity, bupropion has also demonstrated utility in treating pediatric and adult ADHD and in treating sexual disorders/dysfunctions. Bupropion may offer particular utility in treating depression characterized by decreased energy and interest; as an adjunctive antidepressant, with a lower risk of manic switch, for bipolar depression; and for treating depression with comorbid tobacco use disorder, ADHD, obesity, or other substance use disorders. Bupropion may also be used to augment other antidepressants in the treatment of MDD and to reverse SSRI-induced side effects. Its greater tolerability, including low risk of weight gain, minimal sedation, and few sexual side effects, adds to bupropion's value as an effective antidepressant.

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CHAPTER 19

Venlafaxine and Desvenlafaxine

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Venlafaxine and desvenlafaxine are two of the more commonly used members of the serotonin-norepinephrine reuptake inhibitor (SNRI) class of antidepressants. As the first member of the SNRI class to be available to prescribers, venlafaxine became one of the most commonly prescribed antidepressants in the United States across the last 30 years. As their names suggest, venlafaxine and desvenlafaxine are closely related medications: the latter is a commercialized form of the principal metabolite of venlafaxine and, for most people, is likely to convey much of the therapeutic activity of the parent drug. However, in contrast to the analogous relationship between amitriptyline and nortriptyline, desvenlafaxine has not replaced venlafaxine in the pharmacopoeia of antidepressants, perhaps because the potential advantages of the newer drug are largely limited to a relatively small subset of patients, namely those who have trouble metabolizing venlafaxine. As outlined in this chapter, desvenlafaxine nonetheless offers prescribers a potentially useful alternative when an SNRI is clinically indicated and venlafaxine is not a consideration (e.g., provider preference and/or patient history of intolerance).

History and Discovery

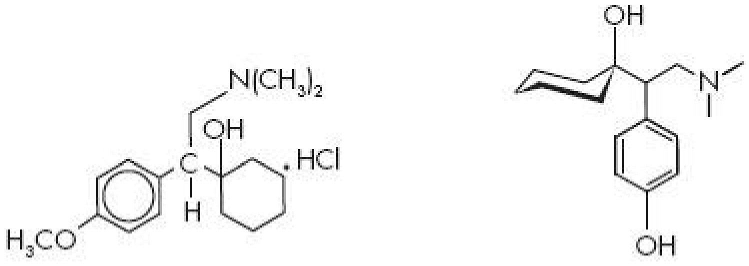
Venlafaxine was developed as the first SNRI in the late 1980s and early 1990s (Bolden-Watson and Richelson 1993; Muth *et al.* 1986). Several early randomized controlled trials (RCTs) suggested that venlafaxine had antidepressant effects comparable to those of tricyclic antidepressants (TCAs), with fewer side effects attributable to anticholinergic and antihistaminergic activity (see, e.g., Einarson *et al.* 1999). An immediate-release (IR) form of venlafaxine was approved by the U.S. FDA for the treatment of major depressive disorder (MDD) in 1994, and the extended-release (XR) formulation was introduced in 1997. Made available after several widely prescribed newer-generation antidepressants (e.g., fluoxetine, sertraline, paroxetine), venlafaxine became one of the leading alternatives for patients who do not respond to selective serotonin reuptake inhibitors (SSRIs).

O-desmethylvenlafaxine (ODV), commonly referred to as desvenlafaxine, is the primary active metabolite of venlafaxine and is also classified as an SNRI. An XR formulation of ODV was developed and tested, and in 2008 desvenlafaxine succinate received FDA approval for use in the treatment of MDD. Compared with venlafaxine, desvenlafaxine has somewhat greater potency for blockade of the norepinephrine transporter (NET), and the succinate formulation has substantially greater bioavailability (Deecher *et al.* 2006).

Generic equivalent products are available for all venlafaxine and desvenlafaxine dosage forms. A new extended-release oral tablet, venlafaxine besylate 112.5 mg (Norwich Pharmaceuticals, Inc.), which has a tablet strength that was not previously available, was approved by the FDA in 2022.

Structure-Activity Relations and Pharmacological Profile

Venlafaxine and desvenlafaxine are bicyclic phenylethylamine compounds and are structurally and chemically unrelated to any other available antidepressants and anxiolytics (Figure 19-1). Venlafaxine and desvenlafaxine inhibit the neuronal reuptake of serotonin (5-HT) and norepinephrine in both in vitro and ex vivo experimental paradigms (Bolden-Watson and Richelson 1993; Muth *et al.* 1986; Owens *et al.* 1997, 2008). Neither drug inhibits monoamine oxidase or has meaningful affinity for muscarinic, cholinergic, histaminergic H_1, or a-adrenergic receptors (Bolden-Watson and Richelson 1993; Muth *et al.* 1986).



Venlafaxine

Desvenlafaxine

FIGURE 19-1. Chemical structures of venlafaxine and desvenlafaxine.

Pharmacokinetics and Disposition

Venlafaxine and desvenlafaxine are well absorbed after oral ingestion and undergo extensive first-pass hepatic metabolism. ODV is the only active metabolite of venlafaxine, and ODV (desvenlafaxine) itself has no active metabolites. Following ingestion of venlafaxine IR, peak plasma concentrations are achieved within 2 hours for venlafaxine and within 3 hours for ODV (Troy *et al.* 1995). Venlafaxine XR is absorbed more slowly than the IR formulation (peak plasma concentrations are achieved within 5.5 hours for venlafaxine and within 9 hours for ODV), which results in lower peak and higher trough plasma concentrations. Steady-state plasma concentrations of both venlafaxine and ODV are reached within 3-4 days of therapy. For extensive (i.e., normal) metabolizers, ODV accounts for at least 70% of the total drug concentration at steady state (Klamerus *et al.* 1992). Venlafaxine and desvenlafaxine exhibit linear kinetics across clinically relevant dosages (i.e., 50-450 mg/day [Klamerus *et al.* 1992]). Both drugs are minimally bound to plasma albumin, and both are primarily eliminated by the kidneys (Howell *et al.* 1993). Clearance of ODV (half-life 10 hours) is slower than that of venlafaxine (half-life 4 hours).

The recommended starting dosage of venlafaxine is 75 mg/day (taken either in divided doses [IR] or once daily [XR]), which is the minimum effective dosage. A lower starting dosage (37.5 mg/day) is often used in older patients or those who have a history of tolerability problems. The maximum approved dosages for the IR and XR formulations are 375 mg/day and 225 mg/day, respectively. The recommended starting dosage of desvenlafaxine is 50 mg/day, which is also the minimum effective dosage; a 25-mg starting dose is available for patients with a history of tolerability problems. The maximum approved dosage is 100 mg/day. Lower dosages of both drugs are recommended for patients with renal insufficiency; lower dosages of venlafaxine are also recommended for patients with liver disease.

Venlafaxine shows a dose-response relationship for efficacy in MDD (Furukawa *et al.* 2019; Thase *et al.* 2006). Desvenlafaxine does not exhibit a positive dose-response curve for efficacy in MDD; drug-versus-placebo differences for 50 mg/day are as large as those observed for higher dosages (Thase *et al.* 2009). It has not been determined whether patients who do not respond to 50 mg/day might benefit from upward titration. As discussed later in this chapter (see "Side Effects and Toxicology"), there is a negative dose-response curve for tolerability. This suggests that any potential additional benefit from dosages above 100 mg/day is offset by increased attrition due to side effects.

Mechanism of Action

Venlafaxine and desvenlafaxine are potent inhibitors of 5-HT reuptake at minimum therapeutic dosages; inhibition of norepinephrine reuptake is lower at these dosages (Bolden-Watson and Richelson 1993; Deecher *et al.* 2006; Owens *et al.* 2008; Vaishnavi *et al.* 2004). Studies using PET to estimate receptor occupancy demonstrate that the minimum effective total daily dose of venlafaxine (75 mg) yields about 80% occupancy of the 5-HT transporter (Voineskos *et al.* 2007). It is thought that the ascending dose-response relationship of venlafaxine is linked to a dose-dependent increase in NET occupancy (Thase and Sloan 2006). Although experimental (Aldosary *et al.* 2022; Harvey *et al.* 2000) and clinical (Davidson *et al.* 2005; Furukawa *et al.* 2019; Thase 1998; Thase *et al.* 2006) data support this hypothesis, significant effects on autonomic measures of noradrenergic function are evident in healthy volunteers at venlafaxine

dosages presumed to be 5-HT selective (i.e., 37.5 mg/day and 75 mg/day [Bitsios *et al.* 1999; Siepmann *et al.* 2007]). One small PET study of venlafaxine-treated depressed patients found a wide range of NET occupancy values, extending from 8% to 61% (Arakawa *et al.* 2019). There is no consensus about the optimal degree of NET inhibition during SNRI therapy.

Indications and Efficacy

Venlafaxine is approved by the FDA for the treatment of MDD, generalized anxiety disorder (GAD), social anxiety disorder, and panic disorder. Desvenlafaxine is approved only for the treatment of MDD.

Major Depressive Disorder

Venlafaxine's antidepressant efficacy at dosages ranging from 75 mg/day to 375 mg/day was established in a large number of RCTs (see Thase and Sloan 2006 for a review). Meta-analyses of studies using active comparators concluded that venlafaxine is one of the more effective newer-generation antidepressants (Cipriani *et al.* 2018; Nemeroff *et al.* 2008; Schueler *et al.* 2011; Smith *et al.* 2002; Thase *et al.* 2001). However, evidence of venlafaxine's superiority over the SSRIs as a class is largely dependent on the large proportion of early studies that used fluoxetine (Cipriani *et al.* 2018; Nemeroff *et al.* 2008), and escitalopram and paroxetine appear to be as effective as venlafaxine in one comprehensive network meta-analysis (Cipriani *et al.* 2018).

The antidepressant efficacy advantage of desvenlafaxine over placebo was established at dosages ranging from 50 mg/day to 400 mg/day (Kornstein *et al.* 2014; Norman and Olver 2021; Thase *et al.* 2009). Only a handful of studies have compared desvenlafaxine with other active antidepressants, and there has been no evidence for its greater efficacy (Cipriani *et al.* 2018; Norman and Olver 2021). A meta-analysis of studies of desvenlafaxine at approved dosages (50-100 mg/day) concluded that its efficacy was similar to that of venlafaxine XR at comparable dosages (i.e., 75-225 mg/day [Coleman *et al.* 2012]).

With respect to other newer antidepressants, venlafaxine has been compared with mirtazapine (Benkert *et al.* 2006; Guelfi *et al.* 2001), bupropion (Hewett *et al.* 2010; Thase *et al.* 2006), duloxetine (Perahia *et al.* 2008), agomelatine (Kennedy *et al.* 2008), and vortioxetine (Alvarez *et al.* 2012; Wang *et al.* 2015). Overall, the results of these studies do not support the hypothesis that venlafaxine routinely conveys an efficacy advantage over other non-SSRI options. Furthermore, the results of these studies suggest that various non-SSRI antidepressants may offer certain tolerability advantages over venlafaxine. For example, in comparison with venlafaxine, mirtazapine and agomelatine were more effective in treating insomnia, agomelatine and bupropion caused less treatment-emergent sexual dysfunction, and vortioxetine produced fewer noradrenergically mediated side effects (e.g., light-headedness [Wang *et al.* 2015]).

Neither venlafaxine nor desvenlafaxine has established efficacy for the treatment of bipolar depression. In one comparative study in patients with bipolar I depression who were being treated with mood stabilizers, adjunctive venlafaxine was associated with somewhat higher rates of treatment-emergent affective switches in comparison with adjunctive paroxetine (Vieta *et al.* 2002). A higher switch rate for venlafaxine was also observed in a study using adjunctive sertraline and bupropion as comparators (Post *et al.* 2006). However, in two studies of bipolar II depression, venlafaxine monotherapy was more efficacious than lithium monotherapy with no greater risk of mood switches (Amsterdam and Shults 2008; Amsterdam *et al.* 2016). Although it is difficult to reconcile these findings, these results do suggest that a subset of patients within the broader bipolar spectrum can be treated safely and effectively with venlafaxine.

In an era in which most depressed patients are first treated with an SSRI, venlafaxine has for nearly three decades been one of the preferred second-line choices for patients who do not respond to SSRI treatment (Thase and Sloan 2006; Thase *et al.* 2000). A meta-analysis of RCTs of patients with SSRI-resistant depression comparing venlafaxine with other second-line antidepressants confirmed a modest advantage for switching outside the SSRI class (Papakostas *et al.* 2008).

Both venlafaxine and desvenlafaxine have demonstrated preventive efficacy in studies of longer-term therapy of MDD (Boyer *et al.* 2015; Rickels *et al.* 2010a; Simon *et al.* 2004). A large long-term study of patients with recurrent depression similarly demonstrated significant prophylactic effects for venlafaxine (versus placebo) after 12 months (Kocsis *et al.* 2007) and 24 months (Keller *et al.* 2007) of maintenance therapy. This study also included a comparison group treated with fluoxetine. Although results were generally comparable across the continuation phase and during the first year of maintenance treatment, a trend suggesting greater efficacy for venlafaxine emerged during the second year of maintenance therapy (Thase *et al.* 2011).

Generalized Anxiety Disorder

Venlafaxine XR was approved by the FDA for the treatment of GAD on the basis of a series of placebo-controlled RCTs (see Thase and Sloan 2006). Across studies, efficacy was established for dosages ranging from 75 mg/day to 225 mg/day, with little evidence of a dose-response relationship. Sustained efficacy across 12 months was subsequently demonstrated in a study using a classic placebo-controlled discontinuation design (Rickels *et al.* 2010b).

With respect to comparative efficacy, venlafaxine XR therapy was found to be significantly more effective than buspirone on some--although not all--measures in one study (Davidson *et al.* 1999). In another RCT, neither venlafaxine nor diazepam was found to be significantly more effective than placebo (Hackett *et al.* 2003). A more recent network meta-analysis of RCTs found that the efficacy of venlafaxine XR was comparable to that of SSRIs in outpatients with GAD (Slee *et al.* 2019).

Social Anxiety Disorder

Venlafaxine XR was approved for the treatment of social anxiety disorder on the basis of a series of RCTs that confirmed its efficacy and safety relative to placebo across up to 6 months of double-blind therapy (see Thase and Sloan 2006). As was the case with GAD, effective dosages ranged from 75 mg/day to 225 mg/day, with little evidence of an ascending dose-response relationship. A recent network meta-analysis found that the comparative efficacy of venlafaxine XR was nominally lower than that of several of the more widely prescribed SSRIs, including escitalopram, paroxetine, and sertraline (Williams *et al.* 2020).

Panic Disorder

The efficacy of venlafaxine XR in treating panic disorder was demonstrated in three placebo-controlled studies of acute-phase therapy (Bradwejn *et al.* 2005; Pollack *et al.* 2007a, 2007b). These studies, which used a 37.5 mg/day starting dosage to minimize side effects, established an effective dosage range for venlafaxine of 75-225 mg/day. Two of the studies included paroxetine (40 mg/day) as an active comparator (Pollack *et al.* 2007a, 2007b). In the first comparison study, two fixed dosages of venlafaxine XR (75 mg/day or 150 mg/day) were comparable to paroxetine in terms of both efficacy and tolerability (Pollack *et al.* 2007a). In the second comparison study, an RCT in which two fixed dosages (75 mg/day or 225 mg/day) were also used, the higher dosage of venlafaxine was significantly more effective than paroxetine on several secondary outcome measures, including the proportion of patients experiencing complete relief from full-symptom panic attacks (70% vs. 58%; Pollack *et al.* 2007b). Finally, a fourth study using a relapse prevention design demonstrated sustained efficacy for venlafaxine XR across 6 months of therapy (Ferguson *et al.* 2007).

Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder

The efficacy of venlafaxine therapy in treating PTSD was established in two large placebo-controlled studies (Davidson *et al.* 2006a, 2006b). Results of a network meta-analysis suggested efficacy comparable to that of several SSRIs that have been approved by the FDA for this indication (de Moraes Costa *et al.* 2020). Although no pivotal studies of venlafaxine therapy have been conducted among patients with OCD, the results of a 12-week single-blind study indicated that venlafaxine might be at least as effective as clomipramine and significantly better tolerated (Albert *et al.* 2002).

Premenstrual Dysphoric Disorder

A double-blind RCT evaluated the efficacy of venlafaxine IR in the treatment of premenstrual dysphoric disorder in 157 women across four menstrual cycles (Freeman *et al.* 2001). Dosages ranged from 50 mg/day to 200 mg/day, with adjustments for adverse events or lack of efficacy early in each cycle. Analyses of daily symptom rating scores revealed significantly greater improvement in the venlafaxine group compared with the placebo group at endpoint on the primary factors of emotion, function, physical symptoms, and pain.

Vasomotor Symptoms Associated With Menopause

An extensive research program evaluated the efficacy, tolerability, and safety of desvenlafaxine for the treatment of vasomotor symptoms associated with menopause (Sun *et al.* 2013; Tella and Gallagher 2014). Evidence confirmed the efficacy of desvenlafaxine at dosages of at least 100 mg/day and showed safety and tolerability profiles comparable to those seen in studies of MDD. Despite such findings, the FDA has not approved desvenlafaxine for this indication. Although less extensively studied than desvenlafaxine, venlafaxine is also widely used for the treatment of vasomotor symptoms associated with menopause, with an efficacy profile comparable to that of SSRIs (Davari-Tanha *et al.* 2016; Ensrud *et al.* 2015). Likewise, venlafaxine has been shown to be an effective treatment for hot flashes and related symptoms following total hysterectomy in cancer patients (Ramaswami *et al.* 2015).

Treatment of Children and Adolescents

Neither venlafaxine XR nor desvenlafaxine is approved for the treatment of individuals younger than 18 years. Six studies of venlafaxine XR have been published in pediatric populations: a pair of studies in MDD (Emslie *et al.* 2007), two RCTs in GAD (Rynn *et al.* 2007), one study in social anxiety disorder (March *et al.* 2007), and a large RCT in SSRI-resistant depression (Brent *et al.* 2008). For desvenlafaxine, two adequately powered RCTs of children and adolescents have been published (Atkinson *et al.* 2018; Weihs *et al.* 2018).

Results of the depression studies of venlafaxine XR (pooled $N = 334$) indicated that the drug was significantly more effective than placebo among participants ages 12-17 years but not among those ages 7-11 years (Emslie *et al.* 2007). Overall, venlafaxine XR therapy was associated with an increased risk of treatment-emergent suicidal and aggressive behaviors compared with placebo. In the pair of GAD studies (pooled $N = 330$), venlafaxine XR was significantly more effective than placebo in the pooled data set; one study was unequivocally positive, but the other study failed to find a separation between drug and placebo on the primary outcome measure (Rynn *et al.* 2007). In the social anxiety disorder study ($N = 293$), venlafaxine XR was significantly more effective than placebo on both primary and secondary outcome measures (March *et al.* 2007). Finally, in a large National Institute of Mental Health-funded study of adolescents with a history of nonresponse to antidepressant medication, switching to venlafaxine XR therapy was no more effective--and was somewhat less well tolerated--than switching to another SSRI. Both venlafaxine XR and SSRIs were more effective when used in combination with cognitive-behavioral therapy than when used as monotherapy (Brent *et al.* 2008).

Neither RCT of desvenlafaxine demonstrated efficacy in children and adolescents with MDD. The study by Atkinson *et al.* (2018) randomly assigned 363 subjects--109 children (ages 7-11 years) and 254 adolescents (ages 12-17 years)--to 8 weeks of double-blind therapy with either a lower (20-35 mg/day) or higher (25-50 mg/day) dosage of desvenlafaxine or a matched placebo. Although both dosage ranges showed good tolerability and no evidence of treatment-emergent suicidality, neither group experienced a significantly greater reduction in depressive symptoms at week 8 compared with the placebo group. As 55.9% of the subjects in the placebo group had symptom scores that met criteria for a treatment response at study endpoint, this negative trial obviously lacked design sensitivity.

The multicenter RCT by Weihs *et al.* (2018) also randomly assigned children (*n* = 130; ages 7-11 years) and adolescents (*n* = 209; ages 12-17 years) with MDD to 8 weeks of double-blind therapy. In this investigation, desvenlafaxine (25-50 mg/day, based on body weight) and an active comparator, fluoxetine (20 mg/day), were compared with placebo. The two active drugs were comparably well tolerated by children and adolescents, and neither drug was associated with an increase in suicidal thoughts or behaviors during double-blind treatment. The study was judged to be a failed trial because neither active drug group had a significantly greater reduction in depressive symptoms at week 8 compared with the placebo group. Again, signal detection was compromised by a high placebo response rate (62.6% at study endpoint).

Side Effects and Toxicology

The tolerability profiles of venlafaxine and desvenlafaxine include all of the characteristic side effects associated with 5-HT uptake inhibition (i.e., nausea, insomnia, tremor, and sexual dysfunction) as well as side effects attributable to norepinephrine reuptake inhibition (i.e., sweating, light-headedness, and dry mouth); therefore, therapy with these SNRIs is associated with a somewhat higher side-effect burden than is usual with SSRIs (Schueler *et al.* 2011; Thase and Sloan 2006). In a meta-analysis of patient-level data conducted by Nemeroff *et al.* (2008), for example, 11% of the patients treated with venlafaxine withdrew from therapy because of adverse events, compared with 9% of the patients treated with SSRIs. Because relatively low dosages of desvenlafaxine are now recommended, its side-effect profile in controlled studies tends to be more favorable than that of venlafaxine (Coleman *et al.* 2012). Available evidence suggests that rates of sexual side effects with venlafaxine or desvenlafaxine are comparable to those with SSRIs (Clayton *et al.* 2002; Kennedy *et al.* 2000; Montejo *et al.* 2001, 2019; Serretti and Chiesa 2009).

Venlafaxine and desvenlafaxine do not adversely affect cardiac conduction or lower the seizure threshold at therapeutic dosages. Both drugs are associated with small average increases in pulse rate and dose-dependent increases in the risk of elevated blood pressure (Clayton *et al.* 2009; Thase 1998; Thase *et al.* 2015). In older adults, the risk of treatment-emergent hypertension may approach 10% when venlafaxine dosages of 225 mg/day and higher are used (Wathra *et al.* 2020). To mitigate such risks, it is recommended that blood pressure be documented before initiating therapy and periodically checked during ongoing therapy. At higher therapeutic dosages, venlafaxine is also associated with a reduction in heart rate variability (Davidson *et al.* 2005); this effect may be exaggerated when venlafaxine is prescribed in combination with certain other medications, including mirtazapine or quetiapine (Huang *et al.* 2016).

Like SSRIs, venlafaxine is associated with a small but significant increase in bleeding disorders. For example, in studies of the risk of bleeding following childbirth, venlafaxine was associated with an increased risk of postpartum hemorrhage (ranging from 1% to 4% [Gahr *et al.* 2015; Hanley *et al.* 2016; Palmsten *et al.* 2013]). In one study, the risk of bleeding during the final month of pregnancy was greater for SNRIs than for SSRIs (Hanley *et al.* 2016). Such risks have not yet been shown with desvenlafaxine, but given its substantial similarity to venlafaxine, comparable risks are likely to be demonstrated.

There are no adequate, well-controlled studies of either venlafaxine or desvenlafaxine in pregnant women. Both drugs were classified by the FDA as pregnancy Category C drugs at the time of their approval, which indicated that they should be used during pregnancy only if they are clearly clinically indicated. According to the more recent FDA Pregnancy and Lactation Labeling Rule, which went into effect in 2015, the safety of neither drug has been established in pregnancy. Studies completed to date do not document an increased risk of any specific birth defect (Lassen *et al.* 2016; Richardson *et al.* 2019). Venlafaxine and desvenlafaxine are excreted in human breast milk and therefore should not be taken by women who are breastfeeding.

It is well known that abrupt withdrawal of venlafaxine can result in discontinuation-emergent symptoms such as dizziness, dry mouth, insomnia, nausea, nervousness, sweating, anorexia, diarrhea, somnolence, and sensory disturbances (Fava *et al.* 2018; Haddad 2001). Available evidence suggests that in comparison with venlafaxine, desvenlafaxine may have somewhat less problematic discontinuation-emergent symptoms (Montgomery *et al.* 2009). To minimize discontinuation symptoms, therapy should be tapered over several weeks when possible, and prescribers should counsel patients not to abruptly stop taking their antidepressant medication.

A number of fatal overdoses of venlafaxine have been reported; there is less clinical experience with overdoses of desvenlafaxine. In nonfatal overdoses of venlafaxine, electrocardiogram changes (e.g., QT interval prolongation, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered levels of consciousness (ranging from somnolence to coma), serotonin syndrome, and seizures have been reported (Howell *et al.* 2007; Whyte *et al.* 2003).

Findings of studies using pharmacoepidemiological data collected in the United Kingdom suggested that venlafaxine may be more lethal in overdose than SSRIs, albeit less so than TCAs (Buckley and McManus 2002; Hawton *et al.* 2010). Because the statistical measure used in these studies, the Fatal Toxicity Index (Henry 1989), is based on the number of overdose deaths per million prescriptions, findings are subject to use biases, in that the patients who are treated with venlafaxine in the current prescribing environment tend to have more severe and resistant psychiatric illnesses compared with patients who are treated with SSRIs and thus may have a greater inherent suicide risk (Mines *et al.* 2005; Rubino *et al.* 2007). Nevertheless, venlafaxine's apparent higher lethality in overdose might be attributable to adverse effects on the seizure threshold (Whyte *et al.* 2003) and on cardiac conduction (Howell *et al.* 2007) at extremely high plasma levels.

Drug-Drug Interactions

Venlafaxine undergoes extensive metabolism in the liver by the cytochrome P450 (CYP) enzyme system, in particular by the CYP2D6 isoenzyme, which is the pathway for the conversion of venlafaxine into ODV. People who are poor metabolizers of CYP2D6 thus have unusually low plasma levels of the metabolite ODV (Preskorn *et al.* 2009). This effect is amplified among patients who are also poor metabolizers via CYP2C19 (Kringen *et al.* 2020). There is evidence that such patients may be less likely to benefit from treatment with venlafaxine than patients who are normal or extensive metabolizers (Lobello *et al.* 2010; Shams *et al.* 2006). Patients who are known to be poor metabolizers via these CYP enzymes would likely be better candidates for therapy with desvenlafaxine than the parent drug.

In vitro and in vivo studies have shown that venlafaxine and ODV are weak inhibitors of CYP2D6 and cause little or no inhibition of other CYP isoenzymes, including 1A2, 2C9, 2C19, and 3A4 (Ball *et al.* 1997; Oganesian *et al.* 2009; Owen and Nemeroff 1998).

Use of venlafaxine or desvenlafaxine is contraindicated in patients taking monoamine oxidase inhibitors because of the risk of serotonin syndrome. As with TCAs and SSRIs, venlafaxine or desvenlafaxine should not be initiated until 2 weeks after discontinuation of a monoamine oxidase inhibitor, and monoamine oxidase inhibitor therapy should not be initiated until at least 7 days after discontinuation of venlafaxine or desvenlafaxine.

Conclusion

Venlafaxine, the first member of the SNRI class in the United States and much of the world, is one of the more effective newer-generation antidepressants, with an overall safety profile that is intermediate between that of SSRIs and that of TCAs. There is evidence of an efficacy advantage for venlafaxine over fluoxetine and perhaps over several other SSRIs; however, such an advantage has not been specifically demonstrated against escitalopram and paroxetine. Venlafaxine's treatment efficacy has also been established in GAD, social anxiety disorder, and panic disorder, although there is no evidence of greater efficacy compared with SSRIs. Desvenlafaxine, which is approved only for the treatment of MDD, has several advantages relative to venlafaxine, including simpler dosing and metabolism that is not dependent on CYP2D6.

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CHAPTER 20

Duloxetine, Milnacipran, and Levomilnacipran

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Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of monoamine reuptake inhibitors that have been found effective for the treatment of major depressive disorder (MDD). They represent another tool for use by providers in patients who do not respond to selective serotonin reuptake inhibitors (SSRIs), or for whom the side effects of SSRIs are found to be intolerable. In this chapter we provide an overview of the pharmacology and the accumulated evidence for the indications, efficacy, tolerability, and safety of the SNRIs duloxetine, milnacipran, and levomilnacipran.

History and Discovery

Duloxetine was first synthesized in the late 1980s and subsequently patented in 1991. It was approved by the U.S. FDA for the treatment of MDD and diabetic neuropathy in the third quarter of 2004 and has subsequently been approved to treat generalized anxiety disorder (GAD), fibromyalgia, and chronic musculoskeletal pain. This long delay after the initiation of clinical investigations was the result of the drug's initial testing in depressed patients at low dosages of 5-20 mg/day, which were not efficacious. Duloxetine has now received approval almost worldwide.

Milnacipran has been approved by the FDA to treat fibromyalgia but has not received an indication for any psychiatric conditions. However, it has been used to treat depression and has received approvals from other countries for the treatment of depression. Levomilnacipran, the active enantiomer of milnacipran, was approved to treat MDD in the United States in 2013 and in Canada in 2015.

Structure-Activity Relations

Duloxetine, milnacipran, and levomilnacipran (Figure 20-1) are medications with antidepressant properties that can act as inhibitors of both serotonin (5-hydroxytryptamine) and norepinephrine reuptake. Whereas SSRIs target only the serotonin transporter (5-HTT), these dual-acting medications have the potential to inhibit both the 5-HTT and the norepinephrine transporter (NET). Collectively, these three medications belong to the class of medications called SNRIs. Several lines of evidence must be considered, however, to determine at which concentrations SNRIs are indeed effective dual-reuptake inhibitors. This is of crucial importance in estimating their potency in clinical settings.

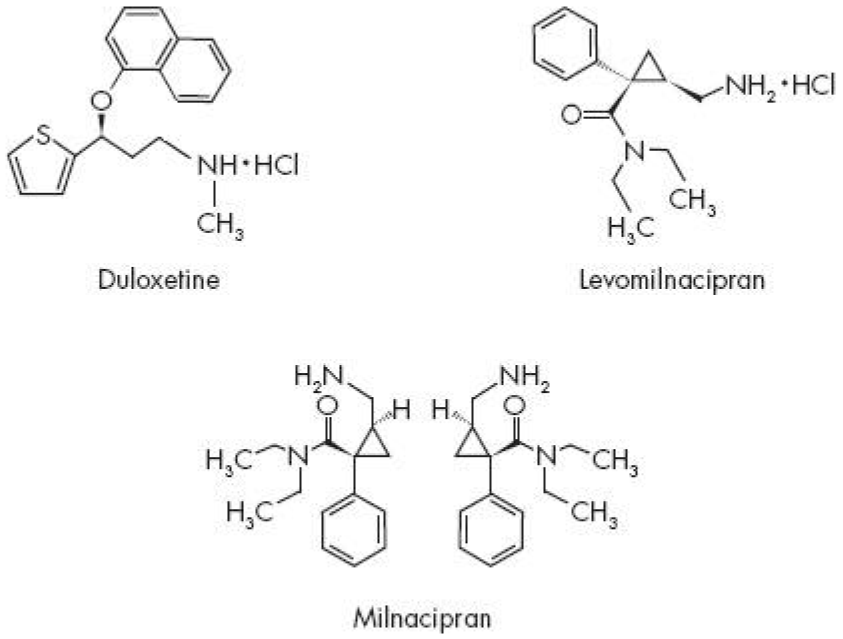
NH•HCl
CH3
Duloxetine
NH2•HCl
CH3
H3C
Levomilnacipran
H2N
NH2
H
H
H3C
H3C
CH3
CH3
Milnacipran

FIGURE 20-1. Chemical structures of duloxetine, milnacipran, and levomilnacipran.

Pharmacological Profile

In Vitro Assessments

The first data to consider in determining the biochemical profile of reuptake inhibitors are their affinity values for membranal carriers. Finding these values involves determining the concentration of a medication necessary to displace 50% of the specific binding of a standard ligand for a given transporter subtype in a cell lysate preparation. This technique generally provides rough estimates of the potential for drugs to inhibit reuptake. Levomilnacipran has stronger affinity for both serotonin and norepinephrine uptake transporters and stronger inhibition of both transporters than does the racemic mixture of milnacipran (Table 20-1).

TABLE 20-1. In vitro affinity and inhibition values for human reuptake transporters by serotonin-norepinephrine reuptake inhibitors

	Serotonin transporter	Norepinephrine transporter	Dopamine transporter
In vitro affinity for uptake transporters, K_i (nM)			
Milnacipran	16.9	139	ND
Duloxetine	0.2	8.9	230[a]
Levomilnacipran	11.2	92.2	ND
In vitro inhibition for uptake transporters, K_i (nM)			
Milnacipran	151	68	ND
Duloxetine	3.7	20	439[a]
Levomilnacipran	16-19	11	ND

Note. ND = not detectable.

[a] Values for duloxetine for the dopamine transporter are not physiologically significant.

Source. Adapted from Auclair *et al.* 2013.

In Vivo Assessments

Ideally, the potency of reuptake inhibitors in animal experiments should be assessed in vivo with the medications administered peripherally. One common technique involves the use of microdialysis studies, in which extracellular levels of neurotransmitters are estimated from the perfusion of artificial cerebrospinal fluid. Data generated with duloxetine indicate that it first increases levels of serotonin in the rat brain, and with escalating dosage it then increases levels of norepinephrine (Koch *et al.* 2003). In the case of milnacipran, levels of serotonin and norepinephrine are generally increased to the same extent (in guinea pigs [Moret and Briley 1997]), although pronounced regional differences have been observed (Bel and Artigas 1999). Levomilnacipran increases rat cortical extracellular levels of norepinephrine and serotonin, with a norepinephrine-to-serotonin potency ratio of 2:1 (Auclair *et al.* 2013).

Potency ratios can also be assessed in vivo with electrophysiological approaches. Specifically, by determining the capacity of reuptake inhibitors to suppress the firing of norepinephrine and serotonin neurons, one can obtain reliable potency estimates. As reuptake transporters are inhibited from their peripheral injection in a dose-dependent manner, there will be an accumulation of serotonin and norepinephrine at the cell body level of those neurons that will activate their respective autoreceptors, thereby decreasing their firing activity. Use of this technique revealed that duloxetine suppresses the firing rate of serotonin neurons by 50% with an intravenous dose of 0.1 mg/kg and suppresses the firing rate of norepinephrine neurons with 0.5 mg/kg (Kasamo *et al.* 1996). This in vivo ratio of 1:5 is quite different from the in vitro affinity ratio of 1:44 (Auclair *et al.* 2013; see Table 20-1). In contrast, use of the same technique revealed that the dose of milnacipran necessary to inhibit the firing rate of serotonin neurons by 50% is 5.7 mg/kg (Mongeau *et al.* 1998). The latter results therefore suggest that milnacipran (and levomilnacipran) is a much less potent inhibitor of serotonin reuptake than is duloxetine.

Assessments of Serotonin and Norepinephrine Reuptake in Humans

Reuptake of neurotransmitters cannot be assessed as directly in humans as it can be in the brains of laboratory animals. However, several approaches can provide useful estimates. For instance, serotonin reuptake inhibition can be estimated with blood platelet uptake of radioactive serotonin, because platelets do not synthesize serotonin and they contain a 5-HTT that is nearly identical to the one present on serotonin neurons in the brain. Because more than 90% of the serotonin present in the blood is in platelets, whole-blood serotonin depletion by a reuptake inhibitor is an even simpler measure. Use of a peripheral (platelet) assay reveals that duloxetine produces a dose-dependent depletion of the serotonin level that reaches about 60% with a dosage of 60 mg/day, an effect still significantly inferior to that seen with 100 mg/day of the tricyclic antidepressant (TCA) clomipramine (Turcotte *et al.* 2001). Milnacipran produces only a 64% inhibition of serotonin uptake with the usual recommended dosage of 100 mg/day (Palmier *et al.* 1989). By comparison, platelet assays revealed that SSRIs produce greater than 80% inhibition of serotonin uptake at clinically effective dosages (Gilmor *et al.* 2002).

Occupancy of the 5-HTT in the human brain can be assessed directly through PET studies using ligands of this transporter labeled with carbon 11. All commonly used SSRIs and venlafaxine produce 80% occupancy of the 5-HTT at their minimum effective dosages in depression (Meyer *et al.* 2004). A duloxetine daily dosage of 60 mg, but not 40 mg, produces a sustained 80% occupancy (Takano *et al.* 2006). PET studies show that daily dosages of milnacipran 100 mg and 200 mg produce 5-HTT occupancies of 40% and 60%, respectively (Nogami *et al.* 2013). To our knowledge, levomilnacipran has not been tested with this approach.

Researchers have attempted to assess occupancy of the NET in the human brain with PET. However, issues remain regarding the specificity of the reboxetine derivative used in several reports (i.e., the lack of a plasma concentration-occupancy relation [Takano *et al.* 2014]). A variety of peripheral measures can, however, be used. In particular, the intravenous tyramine pressor test has produced consistent results. Tyramine penetrates peripheral norepinephrine terminals through the NET and releases norepinephrine in a calcium-independent manner, thereby transiently elevating systolic blood pressure. Any drug that effectively blocks the NET attenuates this pressor response in a dose-dependent manner. Whereas the SSRIs paroxetine and sertraline do not affect pressor response, the TCAs desipramine, nortriptyline, and clomipramine attenuate the pressor response, as do the selective norepinephrine reuptake inhibitors maprotiline, reboxetine, and atomoxetine (Blier *et al.* 2007; Gobbi *et al.* 2003; Harvey *et al.* 2000; Turcotte *et al.* 2001). Venlafaxine significantly attenuates the tyramine response in depressed patients only at dosages in the range of 225-375 mg/day (Blier *et al.* 2010; Debonnel *et al.* 2007). Duloxetine exerts a clear effect starting at 120 mg/day (Vincent *et al.* 2004), whereas milnacipran and levomilnacipran have not yet been tested in this model. A variety of other peripheral measures suggest that duloxetine may begin to inhibit norepinephrine reuptake at 60 mg/day (Chalon *et al.* 2003; Vincent *et al.* 2004).

Taken together, these results obtained in humans indicate that duloxetine is a potent serotonin reuptake inhibitor at 60 mg/day. A recent report found that NET occupancy by duloxetine was 29.7% at 20 mg, 30.5% at 40 mg, and 40.0% at 60 mg. The estimated dose of duloxetine inducing 50% NET occupancy was 76.8 mg, and the estimated plasma drug concentration inducing 50% NET occupancy was 58.0 ng/mL (Moriguchi *et al.* 2017).

Milnacipran appears to preferentially block norepinephrine reuptake, as has easily been demonstrated in the brains of laboratory animals even at low doses (Bel and Artigas 1999; Mongeau *et al.* 1998), whereas blockade of serotonin reuptake can only be documented with high doses. In humans, robust serotonin reuptake inhibition (> 80% transporter blockade) appears to be achieved only with supratherapeutic doses (i.e., 300-400 mg; Palmier *et al.* 1989). Similar preclinical results have been obtained with levomilnacipran (Auclair *et al.* 2013).

Mechanism of Action

SNRIs produce rapid inhibition of reuptake transporters in the brain, but their antidepressant effects are generally not seen for at least 2 weeks. Extensive electrophysiological and microdialysis studies in laboratory animals have consistently shown a similar delay before SNRIs produce a net enhancement of serotonin and/or norepinephrine transmission (see Blier 2006 for a review). This delay may occur because, as a result of 5-HTT inhibition, potent serotonin reuptake inhibitors initially suppress the firing of serotonin neurons through activation of serotonin type 1A autoreceptors on neuron cell bodies. After 2-3 weeks of sustained administration, these autoreceptors desensitize, and the serotonin neuronal firing rate returns to normal. At this point, there is a net enhancement of serotonin transmission in the forebrain (Blier and De Montigny 1983).

In the case of drugs that inhibit the NET, the firing rate of norepinephrine neurons is promptly diminished through activation of a_2-adrenergic autoreceptors on neuron cell bodies. After 2-3 weeks of sustained administration, the firing rate remains attenuated because the cell body a_2-adrenergic autoreceptors do not become desensitized. In contrast, a_2-adrenergic autoreceptors on norepinephrine terminals generally become desensitized with sustained administration, which leads to a net enhancement of norepinephrine transmission in the forebrain (Invernizzi and Garattini 2004; Rueter *et al.* 1998a, 1998b; Szabo and Blier 2001).

Pharmacokinetics and Disposition

Absorption and Distribution

Table 20-2 summarizes the pharmacokinetics of duloxetine, milnacipran, and levomilnacipran.

TABLE 20-2. Pharmacokinetics of duloxetine, milnacipran, and levomilnacipran

Medication	Half-life	Time to steady state	CYP enzyme(s) inhibited	Kinetics
Duloxetine	12 hours	3 days	1A2 (potent) 2D6 (potent)	Linear
Milnacipran	8 hours	2 days	None	Linear
Levomilnacipran	12 hours	3 days	3A4	Linear

Note. CYP = cytochrome P450.

Duloxetine

Duloxetine is available in capsules that contain enteric-coated pellets. According to current product labeling, Cymbalta capsules and generic equivalents should be swallowed whole and not chewed, crushed, sprinkled on food, or mixed with liquids (Eli Lilly 2017). Drizalma capsules can be administered whole; can be opened and the pellets sprinkled on applesauce; or can be mixed with water for nasogastric tube administration (Sun Pharmaceutical 2019). Full instructions are provided in the product labeling. Duloxetine is rapidly absorbed after oral administration, and its absorption is not altered by food. Duloxetine's plasma level is proportional to dose, up to a maximum of 60 mg twice daily. It is highly (about 90%) bound to its plasma proteins. Its plasma elimination half-life is approximately 12 hours (Sharma *et al.* 2000). With repeated administration, duloxetine takes approximately 3 days to reach a steady-state level.

Milnacipran and Levomilnacipran

Milnacipran and levomilnacipran have low (13% and 22%, respectively) and nonsaturable plasma protein binding. They are rapidly absorbed after oral administration and have high bioavailability, and their absorption is not affected by food intake. They have no active metabolites, and their elimination half-life is 8 hours. Steady-state levels are thus achieved within 3 days, with no drug accumulation occurring during prolonged dosing, and milnacipran and levomilnacipran are cleared from the body within 3 days of treatment cessation.

Metabolism and Elimination

Duloxetine

Duloxetine is extensively metabolized through various pathways (Skinner *et al.* 2003). Numerous metabolites are found in circulation, none of which is believed to contribute to duloxetine's therapeutic activity. Duloxetine is metabolized mainly by cytochrome P450 (CYP) 1A2 and 2D6 isoenzymes.

Milnacipran and Levomilnacipran

The CYP system is not involved in the metabolism of milnacipran or levomilnacipran (Briley 1998; Chen *et al.* 2015). However, these compounds are inhibitors of CYP3A4, and levomilnacipran at high dosages can interact with other CYP3A4 inhibitors (Allergan 2019; Forest Pharmaceuticals 2009; Hiemke *et al.* 2018). The metabolism of milnacipran

and levomilnacipran is mainly mediated through phase II conjugation. Milnacipran and levomilnacipran are eliminated by the kidneys; approximately 50%-60% of the drugs are recovered in the urine as parent compounds and 20% as their glucuronide conjugates. The remainder of the metabolites are excreted mainly as an *N*-dealkyl metabolite and its glucuronide conjugate and in negligible amounts as an *N*-didealkyl metabolite and a hydroxy metabolite (Brunner *et al.* 2015; Chen *et al.* 2015; Puozzo and Leonard 1996; Puozzo *et al.* 2002).

Indications and Efficacy

Duloxetine is FDA approved for use in the treatment of MDD, GAD, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain. Although milnacipran is used for the treatment of MDD in various countries, it has not yet received FDA approval for that indication. In the United States, milnacipran is approved only for the treatment of fibromyalgia. Levomilnacipran is approved only for the treatment of MDD. Clinical practice has shown us the efficacy of these two molecules in both conditions, despite the lack of controlled studies, because of the fact that levomilnacipran is the active enantiomer of milnacipran.

It is recommended that dosing for duloxetine start at 20 mg bid and increase to 40-60 mg/day (the target dosage) within 1 week. The maximum recommended dosage is 120 mg/day. For milnacipran, dosing should begin at 12.5 mg for day 1; increase to 25 mg (12.5 mg twice daily) for days 2 and 3; and increase to 50 mg (25 mg twice daily) for days 4-7. The dosage may then be increased by 50 mg/week to a target dosage of 100 mg/day. The maximum recommended dosage of milnacipran in fibromyalgia is 200 mg/day. For levomilnacipran, the starting dosage is 20 mg/day (taken in a single dose), but it is recommended that this be increased to 40 mg/day (the minimum effective dosage) after 2 days. The dosage can then be increased, over intervals of 2 or more days, to 80 mg/day and then to 120 mg/day, according to tolerability and response. Table 20-3 provides the formulations and dosing for duloxetine, milnacipran, and levomilnacipran as described in the manufacturers' prescribing information.

TABLE 20-3. Indications, formulations, and dosing for duloxetine, milnacipran, and levomilnacipran

Medication	Indications	Formulations	Initial dosage[a]	Target daily dosage[a]	Max. daily dosage[a]

Note. All dosing is in milligrams.

ER = extended release; GAD = generalized anxiety disorder; MDD = major depressive disorder.

[a] See section "Indications and Efficacy" for more details.

[b] Cymbalta capsules must be swallowed whole and not opened or chewed.

[c] Drizalma SprinkleTM capsules may be swallowed whole, may be opened and sprinkled over applesauce, or may be administered via nasogastric tube (see product labeling).

Medication	**Indications**	**Formulations**	**Initial dosage[a]**	**Target daily dosage[a]**	**Max. daily dosage[a]**
Duloxetine	MDD	Cymbalta delayed-release capsule[b]: 20, 30, 60	20 bid	40-60	120
	GAD	Drizalma SprinkleTM delayed-release capsule[c]: 20, 30, 40, 60			
	Diabetic peripheral neuropathic pain				
	Fibromyalgia				
Chronic musculoskeletal pain					
Milnacipran	Fibromyalgia	Tablet: 12.5, 25, 50, 100	Day 1: 12.5 Days 2-3: 25	100	200

Note. All dosing is in milligrams.

ER = extended release; GAD = generalized anxiety disorder; MDD = major depressive disorder.

[a] See section "Indications and Efficacy" for more details.

[b] Cymbalta capsules must be swallowed whole and not opened or chewed.

[c] Drizalma SprinkleTM capsules may be swallowed whole, may be opened and sprinkled over applesauce, or may be administered via nasogastric tube (see product labeling).

Medication	Indications	Formulations	Initial dosage[a]	Target daily dosage[a]	Max. daily dosage[a]
			Days 4-7: 50		
Levomilnacipran	MDD	Capsule ER: 20, 40, 80, 120	20 bid for 2 days, then 40 bid	40-120	120

Note. All dosing is in milligrams.

ER = extended release; GAD = generalized anxiety disorder; MDD = major depressive disorder.

[a] See section "Indications and Efficacy" for more details.

[b] Cymbalta capsules must be swallowed whole and not opened or chewed.

[c] Drizalma SprinkleTM capsules may be swallowed whole, may be opened and sprinkled over applesauce, or may be administered via nasogastric tube (see product labeling).

Major Depressive Disorder

Duloxetine

Duloxetine has been extensively evaluated in placebo-controlled studies as well as active comparator studies of the efficacy and safety of its antidepressant action. An extensive systematic review by Rodrigues-Amorim *et al.* (2020) provided support for the safety and efficacy of duloxetine for treating MDD. Head-to-head comparisons with SSRIs and SNRIs have yielded mixed results, which appear to be influenced by dosing regimens (Cipriani *et al.* 2012; Rodrigues-Amorim *et al.* 2020). Overall, no statistically significant difference in efficacy has been found between duloxetine and other drugs used to treat MDD.

Milnacipran

A meta-analysis of three short-term (4-to 8-week) double-blind, acute efficacy multicenter trials in inpatients and outpatients with moderate to severe depression concluded

that milnacipran provides a superior antidepressant effect compared with placebo at dosages of 50 mg and 100 mg twice daily but not at a dosage of 25 mg twice daily (Lecrubier *et al.* 1996; Macher *et al.* 1989).

Several studies have compared milnacipran with SSRIs or TCAs. Milnacipran was noted to have equal efficacy but superior tolerability relative to the TCA imipramine (Puech *et al.* 1997). Two meta-analyses concluded that evidence was insufficient to suggest a difference in response rates between milnacipran and any SSRI (Nakagawa *et al.* 2009; Papakostas and Fava 2007). A 24-week randomized, double-blind study demonstrated the safety, tolerability, and efficacy of flexible dosages of milnacipran and venlafaxine (100-200 mg/day) in treating MDD (Olie *et al.* 2010).

Levomilnacipran

Four of five controlled studies (involving a total of 3,020 patients) reported effectiveness for the 40-120 mg/day dosage range of levomilnacipran in patients with MDD ages 18-80 years. No controlled active comparator study has yet been published (Faquih *et al.* 2019; Wagner *et al.* 2018).

Generalized Anxiety Disorder

Duloxetine

Duloxetine was shown to be effective in reducing symptoms of GAD in 11 placebo-controlled trials (reviewed in Rodrigues-Amorim *et al.* 2020). Furthermore, duloxetine was found to be more effective and better tolerated compared with other antidepressants (i.e., escitalopram and venlafaxine).

Milnacipran and Levomilnacipran

No studies to date have examined milnacipran or levomilnacipran for the treatment of GAD.

Neuropathic and Chronic Pain

Duloxetine

TCAs and SNRIs clearly produce significant relief of physical symptoms, such as pain in depression and in a variety of pain syndromes (Stahl *et al.* 2005). Duloxetine exerts a prompt and substantial analgesic effect over and above its antidepressant action (Perahia *et al.* 2006). Potentiation of the activity of serotonin and norepinephrine is believed to result in the inhibition of central pain through descending modulatory pathways (Sussman 2003).

In an 8-week study, duloxetine at a fixed dosage of 60 mg/day significantly reduced pain measures from baseline to endpoint compared with placebo in patients with MDD and at least moderate pain. At 8 weeks, the mean average pain score on the Brief Pain Inventory--Short Form was close to 3, which can be considered a mild level of pain compared with the moderate or higher levels of pain indicated by baseline scores (5.8 [Brecht *et al.* 2007]). Similarly, elderly patients with depression who received duloxetine 60 mg/day for 8 weeks showed significantly greater improvement in back pain scores and the amount of time in pain compared with patients who received placebo (Raskin *et al.* 2007). In a randomized controlled trial evaluating the efficacy of duloxetine 60 mg/day in patients with MDD and associated painful physical symptoms, the drug was superior to placebo in reducing overall, shoulder, and back pain as well as time spent in pain (Detke *et al.* 2002b).

Duloxetine has also been shown to be effective in the management of postoperative pain. In a recent meta-analysis of 13 studies, duloxetine led to decreased postoperative pain at 24 and 48 hours as well as decreased opioid use at 24 and 48 hours. Postoperative conditions studied included lumbar surgery, hysterectomy, hip surgery, knee replacement, gynecological surgery, and mastectomy (de Oliveira Filho *et al.* 2020).

Milnacipran and Levomilnacipran

The capacity of milnacipran to relieve chronic pain has been reported in open trials. However, in a study of 40 adults with chronic low back pain, there were no significant differences in primary or secondary outcomes between milnacipran 100-200 mg/day and placebo (Derry *et al.* 2015). Another randomized controlled trial comparing milnacipran and placebo for idiopathic neuropathy pain was terminated because of lack

of recruitment (NCT01288937). There have been no studies evaluating levomilnacipran for the treatment of pain.

Fibromyalgia

Duloxetine

Seven randomized controlled trials have examined the safety and efficacy of duloxetine for the treatment of pain associated with fibromyalgia, and all favored duloxetine. In a meta-analysis of these studies, which included 2,642 adults with fibromyalgia, treatment with duloxetine led to greater pain relief than placebo. However, the use of duloxetine was associated with more adverse events. Dosing at 60 mg/day led to fewer withdrawal effects than 120 mg/day (Lian *et al.* 2020). A recent study of juvenile fibromyalgia in 184 youth had mixed results. Although duloxetine was not more effective than placebo in terms of pain severity at 24 hours, significantly more youth who received duloxetine had [?] 30% and [?] 50% reductions in pain severity than those who received placebo (Upadhyaya *et al.* 2019).

Milnacipran and Levomilnacipran

An initial placebo-controlled study of milnacipran in fibromyalgia patients found that 37% of those who received 100 mg of milnacipran twice daily experienced a significant reduction (50% or more) in pain intensity compared with 14% of those who received placebo (Vitton *et al.* 2004). Subsequent studies led to milnacipran's approval in the United States for treating fibromyalgia (Hauser *et al.* 2011). There have been no studies evaluating levomilnacipran in the treatment of pain.

Stress Urinary Incontinence

Duloxetine has been shown to be efficacious in the treatment of stress urinary incontinence, with 40 mg twice daily being the recommended dosage (Li *et al.* 2013). Serotonin and norepinephrine increase excitatory glutamate transmission in Onuf's nucleus in the sacral spinal cord, which facilitates urethral sphincter contraction (Thor 2003). This presumably is the mechanism underlying duloxetine's beneficial effects in the treatment of this problem.

Side Effects and Toxicology

Duloxetine

The safety and tolerability of duloxetine at a dosage range of 40-120 mg/day have been assessed in a number of clinical trials. In an 8-month study, the most common treatment-emergent adverse events were nausea, dry mouth, vomiting, yawning, and night sweats (Pigott *et al.* 2007). Most of these effects emerged early, within the first 8 weeks of treatment. Other studies have reported insomnia, somnolence, headaches, ejaculation disorders, diarrhea, constipation, and dizziness as common adverse events with duloxetine use (Detke *et al.* 2002a, 2002b; Khan *et al.* 2007; Nierenberg *et al.* 2007).

The incidence of nausea associated with duloxetine appears to be comparable to that associated with other SSRIs and SNRIs. Nausea is transient and is usually experienced

on treatment initiation. A starting dosage of 60 mg/day appears to provide the best combination of clinical response and tolerability (Bech *et al.* 2006; Pritchett *et al.* 2007). Clinicians may, however, consider starting at a lower dosage (30 mg/day) for patients in whom tolerance is a concern. A tolerability study of duloxetine in 137 patients found a starting dosage of 30 mg/day to be associated with a lower rate of nausea than a starting dosage of 60 mg/day (16% vs. 33%, respectively) (Dunner *et al.* 2005). A separate study including 4,313 patients found the 30 mg/day starting dosage to be preferred by the majority of female patients (Wilhelm *et al.* 2012). The initial tolerability of duloxetine 60 mg/day can be improved if the drug is taken with food; when taken with food, the 60 mg/day initial dosage has tolerability comparable to an initial dosage of 30 mg/day (Whitmyer *et al.* 2007).

Duloxetine has not been associated with weight gain, and in fact in one study it was noted to be associated with a mean weight loss of 1 kg (Nierenberg *et al.* 2007). This decrease significantly differed from the lack of effect that placebo and escitalopram had on weight.

Changes in blood pressure and heart rate associated with duloxetine treatment do not appear to be clinically significant. Pooled data from 735 patients receiving duloxetine 40-120 mg/day showed that 0.7% experienced a 10 mm Hg increase in systolic or diastolic blood pressure versus 0.4% of patients receiving placebo. Heart rate was increased by less than 1 beat per minute (Schatzberg 2003).

Rates of sexual dysfunction, including anorgasmia, erectile dysfunction, delayed ejaculation, and decreased libido, appear to be low with duloxetine. Researchers found that after 8 months, categorical outcomes shown on a questionnaire about changes in sexual functioning did not differ significantly between duloxetine-and escitalopram-treated groups (Pigott *et al.* 2007). In clinical practice, however, any drug that strongly inhibits serotonin reuptake has the potential to cause problematic sexual dysfunction in a significant proportion of patients.

A significantly higher rate of discontinuation of treatment was reported among patients who were randomly assigned to receive duloxetine compared with those who were assigned to receive escitalopram or venlafaxine (Cipriani *et al.* 2012). It appears that study participants who discontinue duloxetine because of adverse events often do so early on in treatment (Nierenberg *et al.* 2007; Perahia *et al.* 2008; Pigott *et al.* 2007), which may indicate poorer initial tolerability.

A systematic search of accumulated data for in utero exposure to duloxetine identified 16 major congenital malformations occurring in 668 infants, yielding a relative risk estimate of 0.8 (Lassen *et al.* 2016). Infant exposure to duloxetine through breast milk is less than 1% of the maternal weight-adjusted dosage (Andrade 2014). These figures suggest that duloxetine can be safely used during pregnancy and lactation.

Milnacipran and Levomilnacipran

An analysis of a database of more than 3,300 patients concluded that the adverse event profile of milnacipran in MDD was comparable to that of SSRIs, except that SSRIs were associated with a higher frequency of nausea and anxiety, whereas milnacipran was associated with a higher incidence of dysuria (Puech *et al.* 1997). Weight gain is uncommon, but sedation may be reported. Although data on rates of sexual dysfunction with milnacipran have not been reported, the incidence is estimated to be low compared with that associated with venlafaxine and SSRIs (Stahl *et al.* 2005). The lower incidence of nausea and sexual dysfunction with milnacipran relative to SSRIs may be taken as indirect evidence of milnacipran's lower potential for serotonin reuptake inhibition, given that these two treatment-emergent adverse events are classically induced by potent serotonin reuptake inhibitors.

Blood pressure increases with milnacipran are minimal. A 12-week randomized, double-blind study comparing milnacipran dosages of 100 mg/day and 200 mg/day versus fluoxetine 20 mg/day in 289 depressed inpatients found no significant changes in blood pressure in any of the groups (Guelfi *et al.* 1998). Tachycardia (defined as a heart rate greater than 100 beats per minute) was seen in 0% of patients receiving fluoxetine, 3% of patients receiving milnacipran 100 mg/day, and 6% of patients receiving milnacipran 200 mg/day. A review of more than 4,000 patients taking milnacipran for MDD showed that the mean increase in blood pressure was less than 1 mm Hg, and the mean increase in heart rate was 4 beats per minute (Puech *et al.* 1997). Given that an increase in heart rate is a thumbprint of potent norepinephrine reuptake inhibition, this increase is consistent with the capacity of milnacipran to effectively block norepinephrine reuptake. No cardiotoxicity has been reported with overdoses of up to 2.8 g/day, which is 28 times the recommended daily dosage (Montgomery *et al.* 1996).

An analysis of the long-term safety of milnacipran (in 715 patients with MDD receiving milnacipran for > 6 months and 189 patients receiving it for > 12 months, as reported by Puech *et al.* 1997) concluded that most adverse events appeared within the first 3 months of treatment and that the incidence decreased steadily thereafter. More important, no treatment-emergent adverse events developed during long-term treatment. Other adverse events reported in product labeling include headache, constipation, dizziness, insomnia, hot flushes, hyperhidrosis, and vomiting (Forest Pharmaceuticals 2009).

The adverse event profile of levomilnacipran is similar to that of milnacipran and basically relates to noradrenergic mechanisms. Common side effects include hyperhidrosis, increased heart rate, elevation of blood pressure, urinary hesitancy, constipation, and nausea. These effects are generally of low intensity and seldom lead to discontinuation. The QTc interval remains unaltered at all therapeutic dosages (40-120 mg/day) and is not prolonged to a clinically significant extent at a dosage of 300 mg/day (Asnis and Henderson 2015).

Drug-Drug Interactions

Serotonin syndrome, a serious and potentially lethal pharmacodynamic interaction, can result if milnacipran, levomilnacipran, or duloxetine is taken concomitantly with a monoamine oxidase inhibitor or another serotonergic drug. To avoid this catastrophic outcome, a monoamine oxidase inhibitor must not be initiated until at least 5 days after duloxetine, milnacipran, or levomilnacipran has been discontinued. A longer elimination period than that expected from plasma half-life is recommended, because brain elimination generally lags behind plasma elimination. At least a 14-day washout of monoamine oxidase inhibitors must be respected before any SNRI is started.

Use of a serotonin reuptake inhibitor antidepressant with an antiplatelet or anticoagulant drug may potentially increase the risk of bleeding due to the antidepressant's effect on the release of serotonin from platelets.

Duloxetine

Inhibitors of CYP1A2, such as ciprofloxacin, increase plasma levels of duloxetine, and concomitant use may require that duloxetine dosages be reduced or that duloxetine be discontinued. When duloxetine is coadministered with a CYP2D6-inhibiting agent of moderate potency, such as bupropion or diphenhydramine, duloxetine levels may increase. However, such alterations in duloxetine levels are in general not clinically significant.

Duloxetine does not inhibit or induce the activity of the CYP1A2, CYP2C9, or CYP3A4 systems. It does, however, moderately inhibit the activity of the CYP2D6 isoenzyme. If duloxetine is coadministered with a medication metabolized by CYP2D6, clinicians should prescribe dosages that are approximately half those usually recommended for the concomitant medication. Duloxetine does not potentiate the psychotropic effects of ethanol or benzodiazepines.

Milnacipran and Levomilnacipran

If levomilnacipran extended-release capsules are coadministered with agents that are strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, ritonavir), the dosage should not exceed 80 mg once daily (Allergan 2019). Because milnacipran and levomilnacipran are not highly metabolized by CYP pathways, they do not participate in pharmacokinetic drug-drug interactions.

Conclusion

At their minimum effective dosages, duloxetine (60 mg/day) and milnacipran (100 mg/day) potently block the reuptake of serotonin and norepinephrine, respectively. In the case of milnacipran, a 100-mg daily dosage produces suboptimal platelet serotonin reuptake inhibition.

Duloxetine, at its maximum recommended dosage (120 mg/day), and milnacipran, at the upper end of its therapeutic range (200 mg/day), are dual reuptake inhibitors. Consequently, none of the SNRIs currently available can be considered equal reuptake inhibitors. They all show efficacy in the treatment of depression and pain syndromes, with emerging evidence also suggesting a potential role for duloxetine in the treatment of stress urinary incontinence and GAD.

Duloxetine, milnacipran, and levomilnacipran are generally well tolerated, with most adverse effects occurring early in treatment, being mild to moderate in severity, and having a tendency to decrease or disappear with continued treatment.

Either duloxetine or levomilnacipran may be used as a first-line treatment for depression, because these medications are not toxic in overdose, and they can be used at a therapeutic dosage from treatment initiation onward with minimal side effects. Consequently, these drugs may be beneficial in patients whose symptoms have been unresponsive to treatment with SSRIs and/or norepinephrine reuptake inhibitors, provided that they are taken at dosages at the upper end of the therapeutic range.

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CHAPTER 21

Ketamine and Esketamine

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History and Discovery

Ketamine emerged from the exploration of phencyclidine derivatives suitable for anesthetic use in humans, and its discovery in 1962 is attributed to Parke-Davis and Dr. Calvin Lee Stevens, a professor of organic chemistry at Wayne State University (Domino *et al.* 1965). Following approval by the FDA in 1970, the drug was used as a battlefield anesthetic for American soldiers during the Vietnam War (Jansen 2000). Early clinicians also recognized ketamine's psychoactive and antidepressant properties (Collier 1972; Domino *et al.* 1965; Lilly 1972; Reier 1971), which led to preliminary psychiatric applications of the drug as an adjunct to psychotherapy in various clinical and research populations (Fontana and Loschi 1974; Grof 1980; Khorramzadeh and Lotfy 1973, 1976; Roquet and Favreau 1981; Sappington *et al.* 1979). However, these same properties contributed to increasing reports of nonmedical use over the next several decades, resulting in federal government classification of ketamine as a Schedule III controlled substance in August 1999 (Ahmed and Petchkovsky 1980; Graeme 2000; Shomer 1992). Ketamine abuse is prevalent internationally, especially in parts of Asia, where it has been considered a large-scale problem (Liao *et al.* 2017). Nonmedical use of ketamine also appears to have doubled in the United Kingdom in the past decade but has decreased or stabilized in other regions (United Nations 2021).

Medically, ketamine continues to be used as a general anesthetic in specific populations, as an analgesic for pain unresponsive to standard treatments, and for off-label use in neurology (Persson 2013). Psychiatric interest in ketamine was revived after positive findings from the first randomized controlled trial (RCT) using ketamine for the treatment of depression (Berman *et al.* 2000) and a larger replication study (Zarate *et al.* 2006). Subsequent trials of ketamine and esketamine--an isomeric form of ketamine--confirmed these findings, culminating in FDA approval and legitimization of esketamine as an antidepressive and antisuicidal agent. Other psychiatric applications of ketamine are currently an area of intense investigation and encompass its use in refractory anxiety, OCD, PTSD, disordered eating, substance use disorders, and as an adjunct to psychotherapy.

At the time of this writing (June 2023), ketamine hydrochloride (Ketalar) injection was available as a sterile solution in vials, at three different concentrations: 10 mg/mL, 50 mg/mL, and 100 mg/mL. Dilution, injection, infusion, and drug compatabilities are described in the product labeling, which must be consulted during preparation (PAR Pharmaceuticals 2021). Generic equivalent products are available for all three ketamine hydrochloride concentrations. Esketamine nasal spray (Spravato) is provided in kits, one kit for each product strength (e.g., a 56-mg dose kit and an 84-mg dose kit); no generic equivalent product is available at present (Janssen Pharmaceuticals 2019).

Structure-Activity Relations

Ketamine (2-[2-chlorophenyl]-2-[methylamino]cyclohexanone) is an arylcycloalkylamine compound that is structurally similar to phencyclidine and cyclohexylamine (Figure 21-1). The freebase form of ketamine is highly lipid soluble and is commercially available as an aqueous preparation of the hydrochloride salt. Ketamine is a chiral compound that exists pharmaceutically as a racemic mixture of *(S)*-ketamine (esketamine) and *(R)*-ketamine (arketamine) enantiomers.

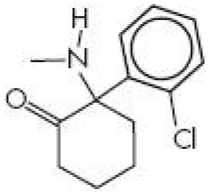

FIGURE 21-1. Chemical structure of ketamine.

Pharmacological Profile

Ketamine has high lipid solubility and low plasma protein binding. It undergoes biotransformation in the liver to norketamine, its primary active metabolite. Approximately 90% of ketamine is excreted in the urine in metabolite form with minimal clearance of unchanged drug, and another 5% undergoes fecal excretion (Clements *et al.* 1982). Ketamine has a wide therapeutic index and has been shown to have a low risk of lethal overdose (Green *et al.* 1999). Its main pharmacological action is on glutamate as an open-channel, nonselective *N*-methyl-D-aspartate (NMDA) receptor antagonist.

Pharmacokinetics and Disposition

Ketamine can be administered by oral, intravenous, intramuscular, subcutaneous, intranasal, epidural, transdermal, intra-articular, and sublingual routes (Kotlinska-Lemieszek

and Luczak 2004). When given orally, ketamine undergoes extensive hepatic biotransformation (via *N*-demethylation by cytochrome P450 [CYP] isoenzymes 3A4, 2C9, and 2B6) into norketamine, the drug's major metabolite. With oral administration of ketamine, norketamine has lower potency than the parent drug but higher plasma levels than those produced when ketamine is given intramuscularly (Grant *et al.* 1981). Hydroxynorketamine, a secondary metabolite also found at high levels soon after administration of ketamine, may play a role in the extended clinical responses that persist after ketamine has been metabolized (Paul *et al.* 2014; Singh *et al.* 2014). Ketamine undergoes renal elimination, and dehydronorketamine is the inactive metabolite that is predominant in urine (Sinner and Graf 2008). The oral bioavailability of ketamine is 17%-20%; bioavailability for other routes is as follows: 25%-50% for intranasal, 30% for sublingual, 30% for rectal, 93% for intramuscular, and approximately 99%-100% for intravenous (Clements *et al.* 1982; Quibell *et al.* 2015). Peak plasma concentrations are reached within 30-60 minutes of oral administration, 5-15 minutes of intramuscular injection, and 1 minute of intravenous injection (Paul *et al.* 2014). Ketamine is rapidly distributed to highly perfused tissues, including the brain, with a distribution half-life of approximately 10-15 minutes and an elimination half-life of 2-2.5 hours (Domino *et al.* 1984). The half-lives of ketamine metabolites are longer than that of the parent drug, measuring 5.3 hours and 6.9 hours for norketamine and dehydronorketamine, respectively (Hijazi *et al.* 2003).

Mechanism of Action

Ketamine is a dissociative anesthetic with analgesic and amnesic properties (Curran and Morgan 2000). The mental state produced by ketamine was originally classified as "dissociative" in an effort to capture the drug's hallucinogenic profile, one that left subjects feeling "disconnected" from their environments (Domino 2010). The term *dissociative* also conveyed the electrophysiological unlinking of thalamoneocortical and limbic systems, thought to be the mechanism by which the drug exerted its primary anesthetic effect on the CNS (Haas and Harper 1992; Jansen 1990; Reich and Silvay 1989).

Ketamine has a complex pharmacological profile, with variable, concentration-dependent affinities for numerous receptors (Alkire *et al.* 2008; Oye *et al.* 1992; Rabiner 2007; Sleigh *et al.* 2014; Smith *et al.* 1981, 1987). Off-target interactions at these receptors are responsible for ketamine's transient cardiovascular, respiratory, and sympathomimetic effects (Domino 2010). Ketamine exerts its primary effect as a voltage-dependent nonselective NMDA receptor antagonist that inhibits the transmembranous flux of calcium and sodium in the presence of the co-agonists glutamate and glycine (Niciu *et al.* 2014). Of ketamine's two enantiomers, *(S)*-ketamine has been shown to have a higher affinity for the NMDA receptor, three-to fourfold greater anesthetic potency, and increased psychotomimetic effects relative to *(R)*-ketamine (Bergman 1999; Jelen *et al.* 2021; Kohrs and Durieux 1998; Wei *et al.* 2020).

It is widely held that ketamine's antidepressant activity occurs via the preferential blockade of NMDA receptors at inhibitory interneurons ("disinhibition hypothesis"), causing disinhibition of pyramidal cells and a burst of excitatory glutamatergic transmission (Duman 2018; Krystal *et al.* 2019; Wei *et al.* 2020). Other proposed NMDA-dependent

mechanisms of action include blockade of spontaneous NMDA receptor-mediated transmission and inhibition of extrasynaptic NMDA receptors by ketamine (Zanos and Gould 2018). However, this central role of NMDA receptors in the treatment of depression has been challenged by preclinical and clinical evidence--that other NMDA receptor antagonists have failed to replicate ketamine's efficacy, for instance (Wei *et al.* 2020; Yang *et al.* 2019). Therefore, mechanisms independent of NMDA receptor inhibition have also been proposed to mediate ketamine's antidepressant action and may include the role of active metabolites, such as hydroxynorketamine (Zanos *et al.* 2016).

Convergent downstream mechanisms and neurotrophic signaling cascades have been implicated in ketamine's antidepressant effects (Deyama and Duman 2020; Wei *et al.* 2020; Yang *et al.* 2019; Zanos and Gould 2018). Relevant and interdependent signaling changes include activation of the non-NMDA glutamate a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, induction of mammalian target of rapamycin signaling, upregulation of brain-derived neurotrophic factor, and resultant synaptic modeling consistent with existing neuroplasticity-related theories of depression (Price and Duman 2020). Although ketamine is known to interact with the opioid system, the clinical relevance of this effect has been debated and warrants further study (Marton *et al.* 2019; Williams *et al.* 2018, 2019; Yoon *et al.* 2019; Zhang and Hashimoto 2019).

Future mechanistic research about ketamine will benefit from novel and integrated approaches to investigation. Some have argued for greater emphasis on circuit-level activity and conceptualizations of ketamine with more nuance than its action at a single, broadly distributed receptor (Heifets and Malenka 2019; Ionescu *et al.* 2018). Initial data suggest that ketamine may alter belief-updating cognitive processes that are thought to maintain certain forms of psychopathology, such as treatment-resistant depression (Bottemanne *et al.* 2022). Furthermore, there has been renewed interest in the relationship between subjective drug experience and treatment efficacy (Ballard and Zarate 2020; Breeksema *et al.* 2023; Kadriu *et al.* 2021; Mathai *et al.* 2020, 2022, 2023; Sumner *et al.* 2021), which appears important for other highly psychoactive therapies such as 3,4-methylenedioxymethamphetamine and psilocybin (Breeksema *et al.* 2020; Vollenweider and Preller 2020).

Indications for and Efficacy of Ketamine

For details on esketamine indications and efficacy, see the later section "Esketamine."

Approved Indications

Anesthesia

Ketamine gained FDA approval in 1970 for the following indications: 1) as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation, 2) for induction of anesthesia before administration of other general anesthetic agents, and 3) to supplement low-potency anesthetic agents, such as nitrous oxide (PAR Pharmaceuticals 2021). Ketamine was an attractive drug for these indications because of its potent anesthetic properties and its safety profile, characterized by a large therapeutic window and low risk of respiratory depression. Recommended dosages for induction of anesthesia are 6.5-13.0 mg/kg intramuscular and 1.0-4.5 mg/kg intravenous, with alternative off-label recommendations for situations that involve administration of adjuvant drugs (Gropper 2019). For maintenance of anesthesia, the manufacturer recommends administering one-half to the full induction dose *or* a continuous infusion of 0.1-0.5 mg/minute of ketamine; however, clinical studies have suggested that higher dosages may be needed to maintain an adequate concentration for anesthesia (White *et al.* 1982). Although only the racemic mixture of ketamine is marketed for this indication in the United States, *(S)*-ketamine was approved in Europe in 1998 and is available in a number of European Union countries for induction and maintenance of general anesthesia, supplementation of local anesthesia, and analgesia in emergency medicine.

Off-Label Applications

Sedation, Analgesia, and Use in Neurology

Various laboratory and clinical studies suggest the utility of ketamine for sedation, analgesia, and improved postoperative outcomes (Adam *et al.* 2005; Green *et al.* 2011; Hocking and Cousins 2003; Menigaux *et al.* 2000; Remerand *et al.* 2009; Zakine *et al.* 2008). Substantial evidence indicates that subanesthetic doses of ketamine are effective in the management of acute postoperative pain, safely reducing opioid requirements during the first 48 hours after surgery and, to a lesser extent, decreasing postoperative nausea and vomiting (Brinck *et al.* 2018). Although there has been some initial support for the use of ketamine for short-term relief of chronic noncancer (e.g., neuropathic, ischemic, fibromyalgia) pain (Michelet *et al.* 2018; Orhurhu *et al.* 2019), more definitive conclusions have been limited by inadequate long-term clinical efficacy and safety data (Bell and Kalso 2018; Cohen *et al.* 2018; Tran and McCormack 2020). A review of ketamine as an analgesic for phantom limb pain was similarly inconclusive (Alviar *et al.* 2016). RCT data (Schwartzman *et al.* 2009; Sigtermans *et al.* 2009) hint at ketamine's benefit in complex regional pain syndrome type 1 at a variety of dosages and routes of administration; however, larger reviews (Azari *et al.* 2012; Zhao *et al.* 2018) suggest that stronger evidence (drawn from larger studies that include data on unsuccessful trials) is needed before ketamine can be recommended for such usage. The evidence for ketamine as an adjuvant for cancer pain has also been explored but is considered inconclusive at this time (Bell *et al.* 2017; Jonkman *et al.* 2017). Neurological applications of ketamine under investigation include its use for migraines, for seizures, and as a neuroprotective agent (Pribish *et al.* 2020).

Relief of Acute Depression and Suicidal Ideation

Multiple meta-analyses have confirmed ketamine's acute antidepressant effects for patients with depressive episodes associated with major depressive disorder (MDD) or bipolar disorder, including reductions in suicidal ideation (Caddy *et al.* 2014; Lee *et al.* 2015; Marcantoni *et al.* 2020; McIntyre *et al.* 2020; Wilkinson *et al.* 2018; Witt *et al.* 2020). Data have shown rapid improvement of depressive symptoms in up to 71% of patients after administration of a single intravenous dose of ketamine (typically 0.5 mg/kg over 40 minutes), with response seen within hours and peak antidepressant effect typically occurring at 24 hours (Aan Het Rot *et al.* 2012; Lee *et al.* 2015; Mathew *et al.* 2012; Salvadore and Singh 2013). Among patients who showed early benefit (within several days) from a single infusion, the mean duration of response was highly variable.

Studies with varying dosages have demonstrated a dose-response relationship for antidepressant effect, with higher doses (0.5-1 mg/kg) of ketamine associated with greater short-term efficacy (Fava *et al.* 2020) and longer time to relapse (Salloum *et al.* 2020). Notably, treatment-dependent adverse effects may also increase with dosage (McIntyre *et al.* 2021). Although it is not yet known which dosages or routes of administration are optimal, there is currently good support for the efficacy of intravenous, intranasal, and oral formulations of ketamine for depression (McIntyre *et al.* 2020). The evidence for intramuscular ketamine is not as well established, but preliminary data suggest this route may also be a safe, practical, and efficacious alternative (Dore *et al.* 2019; Kheirabadi *et al.* 2020; Loo *et al.*

2016). Variables such as provider experience, clinical infrastructure, patient preference, relative costs, accessibility, and other ethical considerations may further guide clinical decision-making (American Society of Ketamine Physicians, Psychotherapists, and Practitioners 2020; McIntyre *et al.* 2021; Singh *et al.* 2017; Wesley and Bennett 2020).

One strategy for extending ketamine's antidepressant benefit has been that of repeat dosing, although the long-term risks and optimal frequency of multiple administrations are unknown (McIntyre *et al.* 2020; Murrough *et al.* 2013; Rasmussen *et al.* 2013). Notably, one study found that twice-weekly dosing did not appear to confer greater benefit than ketamine given thrice weekly (Singh *et al.* 2016). In a Cochrane Review meta-analysis of 25 double-blind and single-blind RCTs (1,242 participants) comparing intravenous administration of 11 different glutamate receptor modulators with placebo, other active psychotropic drugs, or electroconvulsive therapy in adults with unipolar MDD, only ketamine showed a significant effect in reducing the acute symptoms of depression (Caddy *et al.* 2015). Although other NMDA antagonists and glutamatergic modulators have demonstrated antidepressant properties, none to date have replicated ketamine's therapeutic profile and clinical efficacy (Henter *et al.* 2018; Pochwat *et al.* 2019).

Results from individual studies and larger reviews confirm that ketamine achieves a rapid reduction in suicidal ideation, lasting up to 7 days from previous administration and extended by repeat dosing (Domany *et al.* 2020; Murrough *et al.* 2015; Phillips *et al.* 2020; Witt *et al.* 2020). Of note, limited controlled data are available on ketamine's effects for patients with a more severe risk of suicide, such as patients who have been hospitalized for suicidal ideation or a suicide attempt (Price and Mathew 2015).

Investigative Applications in Psychiatry

Ketamine has been investigated for a number of other psychiatric indications beyond depression. A growing body of evidence suggests that ketamine has value in the treatment of refractory anxiety disorders, including generalized anxiety, social anxiety, and anxiety with comorbid depression or bipolar disorder (Banov *et al.* 2020). These effects extend to OCD and PTSD, which are no longer classified as anxiety-spectrum disorders but are acknowledged to feature anxiety as a significant illness component. In a randomized, placebo-controlled crossover trial of ketamine in unmedicated patients with refractory OCD, participants who received ketamine first

showed significant and rapid antiobsessional effects during the 0.5 mg/kg infusion that persisted until 1 week after infusion, compared with participants who began with placebo saline infusion (Rodriguez *et al.* 2013). A subsequent study of the neurochemical effects of ketamine versus saline infusions using proton magnetic resonance spectroscopy suggests that the therapeutic effect of ketamine in OCD may occur independently of glutamate-glutamine activity (Rodriguez *et al.* 2015). Both single (Feder *et al.* 2014) and repeated (Feder *et al.* 2021) doses of ketamine have been efficacious when compared with midazolam for chronic PTSD in small RCTs. Preliminary data also support the utility of ketamine when combined with the opioid antagonist nalmefene for compulsive behavior in eating disorders (Mills *et al.* 1998).

Subanesthetic dosages of ketamine have also been associated with improved outcome for substance use disorders. Studies of cocaine users have shown that ketamine decreases drug use, reduces craving, and increases motivation for treatment (Dakwar *et al.* 2014, 2017, 2019). Increased abstinence rates have been demonstrated with ketamine for opioid (Jovaisa *et al.* 2006; Krupitsky *et al.* 2002, 2007) and alcohol (Dakwar *et al.* 2020; Krupitsky and Grinenko 1997; Wong *et al.* 2015) dependence. Several of these studies have been embedded in a psychotherapeutic context, including motivational, mindfulness-based, and existentially oriented therapies. Others have more broadly considered the value of a psychedelic framework and flexible treatment paradigms in approaching the psychiatric use of ketamine (Bennett 2019; Bravo *et al.* 2021; Dore *et al.* 2019; Lieberman 2021; Ring *et al.* 2016; Sumner *et al.* 2021). It is important to note that these uses are investigational as of the time of this writing (2023).

Side Effects and Toxicology

Ketamine has a wide margin of safety but may be associated with various adverse reactions. At anesthetic dosages of the drug (1-3 mg/kg), "emergence phenomena"--characterized by a range of psychological manifestations including hallucinations, confusion, delirium, vivid imagery, and a prolonged dreamlike state--have occurred in approximately 12% of patients recovering from anesthesia (Green *et al.* 2011). Of note, it is not clear how such phenomena overlap with and differ from altered states of consciousness associated with the therapeutic benefit of other psychedelic treatments (Johnson *et al.* 2019; Sumner *et al.* 2021). Other common side effects ([?] 10%) of ketamine include transient nystagmus, diplopia, hypertension, tachycardia, respiratory stimulation, nausea, vomiting, and skin inflammation or rash. Less common side effects ([?] 1%) include anorexia, bradycardia, cardiac arrhythmia, hypotension, and respiratory depression. In rare cases ([?] 0.1%), anaphylaxis, sialorrhea, laryngospasm, and cystitis have been reported. Ketamine-induced renal dysfunction, ulcerative cystitis, and abdominal pain seem to be more prevalent in frequent, high-dose users (Curran and Morgan 2000).

At the subanesthetic dosages (0.1-1 mg/kg) used in studies investigating ketamine's analgesic and antidepressant properties, psychotomimetic effects are commonly reported, including symptoms of dissociation, perceptual disturbances, abnormal sensations, depersonalization, and derealization, which peak and resolve within 1-2 hours of drug administration (Short *et al.* 2018). These and other subjective experiences associated with acute ketamine administration have correlated positively

with antidepressant response (Mathai *et al.* 2020; Niciu *et al.* 2018; Sumner *et al.* 2021) but are not thought to be necessary or sufficient for outcome (McIntyre *et al.* 2021). Attention to environment, comfort, adaptability, and other contextual variables may best ensure psychological safety and optimize clinical efficacy when dealing with drug-mediated states of consciousness (Johnson *et al.* 2008; McIntyre *et al.* 2021). Other psychiatric effects associated with ketamine include possible worsening of mood or anxiety, leading to discontinuation of treatment for some patients (Short *et al.* 2018). Ketamine dependence has been reported in the scientific literature, and potential for misuse and addiction may be related to its agonist activity at m opioid receptors or to its dopaminergic effects (Lindefors *et al.* 1997; Liu *et al.* 2015; Sanacora and Schatzberg 2015; Xu and Lipsky 2015).

Dizziness, drowsiness, light-headedness, headache, and blurred vision are common neurological effects reported with subanesthetic doses of ketamine. Therefore, patients are advised to arrange alternative transportation for appointments and to not operate motor vehicles or hazardous machinery without at least one night of sleep following the appointment (McIntyre *et al.* 2021). Some evidence exists for mild, acute cognitive disturbances; these should be considered alongside preclinical data suggesting that ketamine may be neurotoxic in certain contexts, based on timing of administration, dosage given, and extent of exposure (Krystal *et al.* 1994; Malhotra *et al.* 1996; Morgan *et al.* 2004; Newcomer *et al.* 1999; Soriano 2012). Studies of ketamine abusers and rodent models have also pointed to adverse effects on brain structure and function under certain conditions of chronic exposure (Liao *et al.* 2011; Schobel *et al.* 2013; Wang *et al.* 2013). Although more long-term data are needed, no persistent or replicable cognitive impairments have been reported among those receiving ketamine in controlled treatment settings (McIntyre *et al.* 2021).

Nausea is the most commonly reported adverse gastrointestinal effect attributed to ketamine (Short *et al.* 2018). Rare cases of hepatoxicity have also been reported. Genitourinary toxicity is uncommon, although lower urinary tract symptoms may increase with cumulative long-term exposure to ketamine (McIntyre *et al.* 2021). Cardiorespiratory effects, including mild stimulation of the cardiovascular system and respiratory depression, have been consistently demonstrated within psychiatric dose ranges (Riva-Posse *et al.* 2018; Rodrigues *et al.* 2020; Szarmach *et al.* 2019). Increases in heart rate or blood pressure appear dose-dependent but are generally minimal, asymptomatic, and transient. However, because some cases may require antihypertensive treatment or result in palpitations, arrhythmias, chest pain, or hypotension, adequate monitoring and medical support should be available during administration. Cardiac function should be continually monitored for high-risk patients (PAR Pharmaceuticals 2021).

Ultimately, ketamine administration for depression should be provided in settings with expertise in both psychiatric and medical safety (McIntyre *et al.* 2021). Acute side effects commonly occur with ketamine but are largely transient and self-limited. Taken together, these findings suggest that subanesthetic doses of ketamine administered to depressed patients in a controlled setting present a low and acceptable level of risk, although great emphasis must be placed on ongoing clarification of optimal dosage and administration, appropriate patient selection, factors mediating the frequency and severity of adverse effects, abuse potential, and long-term efficacy and safety data.

Drug-Drug Interactions

Drugs such as rifampin and St. John's wort (which are potent inducers of CYP3A4) increase the metabolism and clearance of ketamine--and, to a much greater extent, of norketamine (Mion and Villevieille 2013). Enzyme-inhibiting substances have the opposite effect and include clarithromycin and grapefruit juice (CYP3A4 inhibitors) and ticlopidine (a potent CYP2C19 inhibitor and a weak CYP2B6 inhibitor) (Domino *et al.* 1984). Several studies have also reported ketamine's synergistic effects when administered with other sedatives (Akhavanakbari *et al.* 2014; Eker *et al.* 2011; Hui *et al.* 1995; Lo and Cumming 1975). The clinical relevance of these interactions remains unclear. Though not contraindicated, monoamine oxidase inhibitors, psychostimulants, and other agents with significant hemodynamic activity should be administered with caution when given with ketamine (McIntyre *et al.* 2021). Studies examining whether opioid antagonists interfere with ketamine's antidepressant effect have reported mixed findings (Marton *et al.* 2019; Williams *et al.* 2018). Furthermore, agents that significantly affect glutamate release, such as alcohol, benzodiazepines, and lamotrigine, may theoretically attenuate response to ketamine and therefore warrant further investigation. No absolute drug contraindications exist for ketamine at the time of this writing (2023).

Esketamine

Intranasal esketamine in conjunction with an oral antidepressant is approved by the FDA for adults with treatment-resistant depression and, more recently, for depressive symptoms in adults with MDD with acute suicidal ideation or behavior (Janssen Pharmaceuticals 2019). Regulatory approval has also been granted by the European Medicines Agency and is pending in other parts of the world (McIntyre *et al.* 2021). Although two of three short-term regulatory trials used by the FDA (Studies 3001 and 3005) did not show a statistically significant effect for primary outcome, drug approval was uniquely granted because of the positive results from the remaining short-term trial (Study 3002) and one longer-term randomized withdrawal study (Study 3003) supporting esketamine's efficacy, durability of effect, dosing interval, and safety (Kim *et al.* 2019).

Esketamine carries a black box warning for 1) sedation and dissociation after administration, 2) potential for abuse and misuse, 3) requirement of a Risk Evaluation and Mitigation Strategy (REMS) drug safety program, and 4) increased risk of suicidal thoughts and behaviors in children and young adults taking antidepressants. Information on the REMS program for Spravato is available from the FDA website (www.fda.gov), which hosts a database of all REMS programs and their unique requirements. Patient Medication Guides are also provided as part of the Spravato product labeling (Janssen Pharmaceuticals 2019). Drug dosing involves two phases of administration: induction and maintenance. The first dose (day 1, week 1) is 56 mg, after which the patient receives 56 or 84 mg twice weekly during weeks 1-4 (induction), then 56 or 84 mg once weekly for the following 4 weeks, and then 56 or 84 mg every week or every 2 weeks (maintenance) as needed to maintain individual remission

or response (Janssen Pharmaceuticals 2019). Dosing frequency should be individualized to the least frequent dosing needed to maintain remission/response. Treatment discontinuation is recommended if only minimal response to esketamine is observed after the initial induction phase.

Compared with ketamine, esketamine benefits from FDA approval and robust clinical investigation. However, esketamine and racemic ketamine are thought to share comparable safety profiles (Correia-Melo *et al.* 2020). Importantly, postmarketing data from the FDA Adverse Event Reporting System database signal that serious adverse effects of esketamine may exist, including suicidal ideation and completed suicide (Gastaldon *et al.* 2021). On the basis of these data, combined with evidence of suicides completed on discontinuation of treatment within the esketamine development program, it is recommended that providers carefully monitor psychiatric safety risk during and while transitioning treatment for both ketamine and esketamine (McIntyre *et al.* 2021). No definite conclusions about the relative efficacy of the two drugs can be reached at present, given the heterogeneity of studies and the absence of adequate head-to-head data (McIntyre *et al.* 2020). However, preliminary evidence suggests that ketamine may have superior efficacy and lower dropout rates (Bahji *et al.* 2021; Singh *et al.* 2016). Factors such as cost and access should also be considered in treatment selection.

Conclusion

From its initial use as an anesthetic and analgesic agent, ketamine has evolved as a versatile and consequential drug, uniquely equipped to address a great unmet need in psychiatry. Racemic ketamine and its *(S)*-enantiomer, esketamine, have been established as efficacious treatments for acute depression and suicidal ideation. Other treatment applications appear promising, but for now they remain investigative. Ongoing research is needed to clarify the mechanisms of antidepressant efficacy at subanesthetic dosages of ketamine. Toward this end, early investigations have identified key contributors relevant to ketamine's therapeutic benefit, which include glutamate-dependent and -independent mechanisms, convergent downstream signaling processes, changes in circuit-level activity, and even phenomenological characteristics of acute drug experience. These actions are not mutually exclusive and probably function in a complex and interdependent fashion. Finally, although a growing body of pioneering work supports the safety and tolerability of ketamine, unanswered questions remain, particularly with respect to long-term efficacy and risks. How might we minimize harm and sustain therapeutic benefit? Where does ketamine fit in treatment algorithms? What are predictors of response and individualized success factors? What are important ethical and regulatory considerations? Is ketamine a psychedelic drug? How does ketamine work in conjunction with psychosocial interventions? While we work toward a broader understanding of the drug, ketamine is a powerful tool that relieves suffering today.

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CHAPTER 22

Benzodiazepines

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History and Discovery

Despite adverse publicity and a problematic public image, the most widely prescribed psychiatric medication in the United States over the past two decades is not an antidepressant, an atypical antipsychotic, or a mood stabilizer but the benzodiazepine alprazolam, with more than 48 million prescriptions issued in 2013 (see Grohol 2015; Stahl 2002). There were 92 million prescriptions for benzodiazepines in 2019. Approximately half of those taking benzodiazepines continued taking them for 2 months or more. According to data from a nationally representative survey of 86,186 adults conducted in 2015 and 2016, it is estimated that 30.6 million adult U.S. residents (12.6%) used benzodiazepines in the past year. Of these, 17% reported misuse, with 51% of individuals between 18 and 25 years and 4% of those 65 years or older reporting misuse of benzodiazepines in the past year (Maust *et al.* 2019).

The first benzodiazepine, chlordiazepoxide, was patented in 1959. Diazepam was introduced in 1963, and numerous derivatives of this drug have since been introduced into the market. The triazolobenzodiazepine alprazolam was introduced in 1981 and revolutionized the treatment of anxiety disorders when it was shown to be effective in the treatment of panic disorder (Chouinard *et al.* 1982; Sheehan *et al.* 1982). It was the first benzodiazepine to be approved by the FDA for the treatment of panic disorder. Since then, clonazepam, another high-potency benzodiazepine, also has received approval from the FDA for the treatment of panic disorder.

Benzodiazepines were widely prescribed in the 1960s, 1970s, and 1980s for pathological anxiety by psychiatrists, family practitioners, and internists who knew the drugs were effective and safe when compared with prior anxiolytic medications such as the barbiturates and meprobamate. However, since the 1990s selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have displaced benzodiazepines as the clinician's first choice for the treatment of anxiety disorders (Kramer 1993). The SSRIs and SNRIs are safer and better tolerated than the tricyclic antidepressants and have been shown to be efficacious in several different anxiety disorders. In addition, they do not have the propensity to cause dependence, withdrawal, or alcohol interaction, or the abuse potential, of the benzodiazepines.

Despite their drawbacks, benzodiazepines have continued to be widely prescribed, both as an adjunctive treatment with an SSRI or SNRI and as the primary treatment for a patient with no response or only a partial response to the SSRI or SNRI. As a result, there has been only a small decline in benzodiazepine prescribing since the SSRIs and SNRIs became available (Uhlenhuth *et al.* 1999). One benzodiazepine user in four takes the drug for a year or longer. Among individuals using a benzodiazepine as a hypnotic, 14% reported long-term use (Balter 1991). Rates of use increase with age, from 2.6% among individuals ages 18-35 years to 8.7% among those ages 65-80 years (Olfson *et al.* 2015). In recent years, there has been a shift to greater use of short-half-life benzodiazepines.

Structure-Activity Relations

Currently marketed benzodiazepines are similar to each other in that they all have the 1,4-benzodiazepine ring system. Modification of this ring system results in benzodiazepines with somewhat different properties (Figure 22-1).

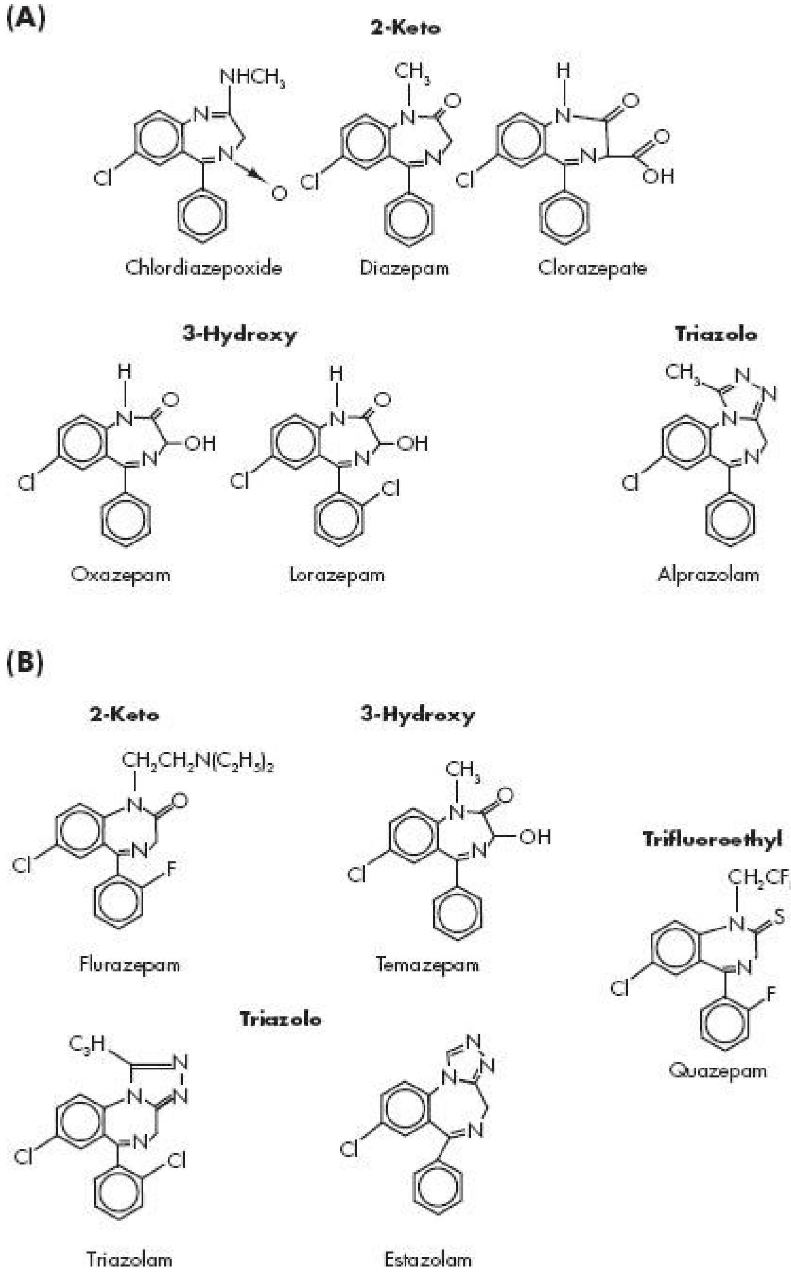
(A)
2-Keto
Chlordiazepoxide
Diazepam
Clorazepate
3-Hydroxy
Triazolo
Oxazepam
Lorazepam
Alprazolam
(B)
2-Keto
3-Hydroxy
Flurazepam
Temazepam
Trifluoroethyl
Quazepam
Triazolo
Triazolam
Estazolam

FIGURE 22-1. Chemical structures of commonly used benzodiazepine (A) anxiolytics and (B) hypnotics.

Pharmacokinetics and Disposition

Knowledge of benzodiazepine pharmacokinetics helps the clinician choose the most appropriate benzodiazepine for the patient and also guides its correct use. Benzodiazepines differ in their pharmacokinetic properties, such as absorption, distribution, and elimination (Table 22-1). On the other hand, all benzodiazepines are similar in that to some degree they all possess anxiolytic, muscle relaxant, sedative-hypnotic, and anticonvulsant properties. The belief that one benzodiazepine is primarily anxiolytic while another is primarily hypnotic is not based on scientific evidence (Greenblatt *et al.* 1983a, 1983b). The preferential selection of a benzodiazepine for one market over another is usually dictated by its pharmacokinetic properties.

TABLE 22-1. Pharmacokinetics of benzodiazepines

Group	**Medication**	**Metabolism**	**Cytochrome P450 (CYP) enzyme(s)**	**Half-life ($t_{1/2}$), hours[a]**
Desmethyldiazepam	Diazepam	Oxidation	2C19, 3A4	26-50
	Bromazepam[XUS]	Oxidation	3A4, 2C19	1-5
	Clorazepate	Oxidation	3A4	40-50
	Prazepam[DISC]	Oxidation	2C19, 3A4	> 21
	Chlordiazepoxide	Oxidation	3A4	> 21 (24-48)
Desalkylflurazepam	Flurazepam	Oxidation	2C19, 3A4	40-120[b]
	Clonazepam	Oxidation	3A4	24-56 (17-60)
Triazolobenzodiazepine	Triazolam	Oxidation	3A4	2-4 (1.5-5.5)
	Alprazolam	Oxidation	3A4	10-15 (6-27)

Note. DISC = Product is FDA approved but all approved generic and brand name products have been discontinued (per the FDA Orange Book [U.S. Food and Drug Administration 2023]); NA = not applicable; XUS = Product not FDA approved at present (August 2023).

[a] Apparent half-life can be dosage form-dependent for sustained-and delayed-release products. Also, half-life may be longer in the setting of overdose, in the presence of other compounds that can inhibit elimination enzyme activity, in the context of impaired organ function, and in other circumstances/settings.

[b] For flurazepam, parent drug 2.3 hours; metabolite 74-113 hours.

Source. Hiemke *et al.* 2018; Lexicomp 2022.

Group	Medication	Metabolism	Cytochrome P450 (CYP) enzyme(s)	Half-life ($t_{1/2}$), hours[a]
	Estazolam	Oxidation	3A4	18
Imidazobenzodiazepine	Midazolam	Oxidation	3A4	1-3 (1.8-6.4)
Thienodiazepine	Brotizolam^{XUS}	Oxidation	3A4	4-8
	Nitrazepam^{XUS}	Reduction	3A4, 2D6	20-50
	Flunitrazepam^{XUS}	Reduction	2C19, 3A4	10-25
Oxazolobenzodiazepine	Oxazepam	Glucuronidation	NA	5-15
	Lorazepam	Glucuronidation	NA	10-20
	Temazepam	Glucuronidation	NA	6-16 (3.5-18.4)

Note. DISC = Product is FDA approved but all approved generic and brand name products have been discontinued (per the FDA Orange Book [U.S. Food and Drug Administration 2023]); NA = not applicable; XUS = Product not FDA approved at present (August 2023).

[a] Apparent half-life can be dosage form-dependent for sustained-and delayed-release products. Also, half-life may be longer in the setting of overdose, in the presence of other compounds that can inhibit elimination enzyme activity, in the context of impaired organ function, and in other circumstances/settings.

[b] For flurazepam, parent drug 2.3 hours; metabolite 74-113 hours.

Source. Hiemke *et al.* 2018; Lexicomp 2022.

Rate of Absorption

Benzodiazepines that are rapidly absorbed from the gastrointestinal tract enter and peak in the circulation quickly and have a quicker onset of action than those that are absorbed more slowly. Diazepam and clorazepate are rapidly absorbed and act quickly, chlordiazepoxide and lorazepam have intermediate rates of absorption and onset of action, and prazepam is slowly absorbed and has a slower onset of action.

Gastrointestinal absorption of benzodiazepines is dictated by intrinsic physiochemical properties of the drug and characteristics of the formulation, such as particle size (Greenblatt *et al.* 1983a, 1983b). Absorption of a benzodiazepine given intramuscularly is dictated by other factors. For example, chlordiazepoxide and lorazepam, when given orally, are absorbed at similar rates in the gastrointestinal tract. When given intramuscularly, lorazepam is more reliably, rapidly, and completely absorbed than chlordiazepoxide (Greenblatt *et al.* 1979, 1982b, 1983a, 1983b).

Lipophilicity

The lipid solubility (lipophilicity) of a benzodiazepine at physiological pH influences the rate at which it crosses the blood-brain barrier by passive diffusion from the circulation, and this, in turn, determines the rapidity of onset of action and intensity of effect (Greenblatt *et al.* 1983a, 1983b). Highly lipophilic drugs cross the blood-brain barrier rapidly, and although all benzodiazepines are highly lipophilic, they differ in their degree of lipophilicity. Because diazepam is more lipophilic than lorazepam or chlordiazepoxide, anxiety reduction and onset of side effects are more rapid.

Duration of Action

With benzodiazepines, the duration of therapeutic action is determined mainly by the rate and extent of drug distribution rather than by the rate of elimination. Benzodiazepine distribution is determined largely by its lipophilicity. Diazepam, which has a longer half-life than lorazepam, has a shorter duration of clinical action after a single dose. The reason is that diazepam, because of its greater lipid solubility, is more extensively distributed to peripheral sites, particularly to fat tissue. Consequently, it is more rapidly moved out of the blood and brain into inactive storage sites, and its CNS effects end more rapidly. Conversely, less lipophilic benzodiazepines maintain their effective brain concentrations longer because they are less extensively distributed to the periphery (Greenblatt *et al.* 1983a, 1983b).

Rate of Elimination

The rate of elimination (i.e., elimination half-life) influences the speed and extent of accumulation and the time to reach a steady state. It also influences the time for drug washout after termination of multiple doses. Accumulation is slow and extensive when the half-life is long. When the rate of metabolic removal equals the rate of ingestion, the drug is said to have reached a steady state. A useful rule is that when treatment has been in progress for at least four times as long as the elimination half-life, the accumulation process is more than 90% complete (Greenblatt *et al.* 1983a, 1983b). When drugs with long elimination half-lives are stopped, they are washed out slowly, and the symptoms recur gradually over a period of days, with less intense or sudden rebound phenomena (Greenblatt *et al.* 1981, 1982a; Kales *et al.* 1982). Side effects from long-term treatment with long-half-life benzodiazepines last longer than with short-half-life benzodiazepines. Because of greater drug accumulation with long-half-life benzodiazepines, frequent drowsiness and sedation are a theoretical concern (Greenblatt *et al.* 1981). Tolerance to sedation occurs with long-term use, even though the plasma drug level remains the same. However, as a matter of caution it is prudent to choose a benzodiazepine with a shorter or intermediate half-life for older adults (Greenblatt *et al.* 1982c), people operating heavy machinery, and those engaging in high-level intellectual tasks.

Biotransformation Pathway

Benzodiazepines are metabolized in the liver by microsomal oxidation or by glucuronide conjugation. Hepatic disease, age, several medical illnesses, and several drugs that impair oxidizing capacity, such as cimetidine, estrogens, and the hydrazine monoamine oxidase inhibitors, all influence the oxidation pathway. These factors

usually magnify the side effects of the benzodiazepine. Consequently, for older adults and patients with liver disease, benzodiazepines that are conjugated (e.g., lorazepam, oxazepam, and temazepam--the LOT trio) are safer than benzodiazepines that are metabolized by oxidation (e.g., diazepam and alprazolam).

Dosing: Sustained-Release Formulations

Dosing schedules of benzodiazepines should be dictated by knowledge about the rate of distribution rather than by information about elimination half-life. Sustained-release formulations of several benzodiazepines have been introduced to provide 24 hours of anxiolysis. In our experience, the sustained-release forms of alprazolam, clorazepate, diazepam, and adinazolam, and the recently approved lorazepam extended-release (XR) formulation, have a duration of therapeutic action of approximately 12 hours, not 24 hours as their indicated use suggests. Standard alprazolam has a duration of action of 4-6 hours, clonazepam has a duration of action of 7 hours, and other standard-formulation benzodiazepines are within this 4-to 7-hour range.

Mechanism of Action

Benzodiazepines produce anxiolysis by their effect on the GABA-benzodiazepine receptor complex. GABA is synthesized from glutamic acid, which is also the most abundant free amino acid in the CNS. Like serotonin, norepinephrine, and dopamine neurons, the presynaptic GABA neuron has a reuptake pump that transports GABA from the synapse for storage or destruction by GABA transaminase. GABA has three target receptors: $GABA_A$, $GABA_B$, and $GABA_C$. The chloride ion channel is controlled by $GABA_A$.

Four distinct pharmacological properties have been described for the benzodiazepine receptor: anxiolytic, hypnotic, anticonvulsant, and muscle relaxation effects. $GABA_A$ receptors with a_2 (or a_3) subunits mediate the anxiolytic effects, whereas $GABA_A$ receptors with an a_1 subunit mediate the sedative-hypnotic actions. Most benzodiazepines interact with both these receptor subtypes. Typically, when GABA occupies the $GABA_A$ receptor site, opening and closing of the chloride channel occur more frequently, and this effect is inhibitory. If at the same time a benzodiazepine binds to the nearby benzodiazepine receptor, the $GABA_A$ receptor is allosterically modulated, and GABA exerts a greater effect (greater frequency of opening and closing) on the chloride channel and conductance. Although GABA works alone at the GABA receptor, the action of GABA is stronger in the presence of a benzodiazepine. The benzodiazepine in the absence of GABA cannot influence the chloride channel by itself.

Therapeutic Uses

Because of their multiple pharmacological actions, benzodiazepines are useful in many areas of medical practice, such as induction of anesthesia, use as a muscle relaxant, and control of seizures. It is beyond the scope of this chapter to elaborate on these nonpsychiatric uses. In psychiatry, benzodiazepines are used to control anxiety, treat insomnia, and acutely manage agitation and withdrawal syndromes.

In the treatment of anxiety disorders, benzodiazepines have a greater effect in some disorders than in others. In panic disorder, they have a significant effect on all dimensions of the illness, with the exception of the core symptoms of depression. Alprazolam, for example, has been shown to be effective in panic disorder at a mean dosage of 5.7 mg/day (range 1-10 mg/day) (Ballenger *et al.* 1988; Chouinard *et al.* 1982; Cross National Collaborative Panic Study, Second Phase Investigators 1992; Sheehan *et al.* 1982, 1984, 1993). Rapid improvement was seen within the first week in the form of decreased panic attacks, phobic fears and avoidance, anticipatory anxiety, and disability. These benefits were shown to persist during a follow-up period of 8 months (Schweizer *et al.* 1993). Efficacy also has been established for lorazepam (Rickels and Schweizer 1986) and clonazepam (Pollack *et al.* 1993; Tesar *et al.* 1991). In the latter studies, clonazepam 2.5 mg/day was as effective and well tolerated as alprazolam 5.3 mg/day.

Despite the well-documented efficacy of benzodiazepines in panic disorder, they have been displaced in clinical practice by the SSRIs and SNRIs. However, some clinicians initiate treatment with both classes of drug simultaneously and then withdraw the benzodiazepine after 6 weeks. The benefits and practicality of this approach to treating panic disorder are reinforced by the findings from two studies (Goddard *et al.* 2001, 2008). The American Psychiatric Association Work Group on Panic Disorder (1998) guidelines for the treatment of panic disorder recommending SSRI monotherapy as the treatment of first choice have failed to achieve traction, as shown by the finding that more than two-thirds of the SSRI prescriptions in 2008 were accompanied by a concomitant benzodiazepine (Keller and Craske 2008). The study by Goddard *et al.* (2008) lends justification to the rationale for using the combination treatment more frequently and for considering it a reasonable alternative first-line treatment for many patients with panic disorder.

Three double-blind studies have shown the efficacy of benzodiazepines in the treatment of social phobia (i.e., DSM-5-TR [American Psychiatric Association 2022] social anxiety disorder) (Davidson *et al.* 1993; Gelernter *et al.* 1991; Versiani *et al.* 1997).

In a double-blind, placebo-controlled study, Rickels *et al.* (1993) found that the tricyclic antidepressant imipramine was better than diazepam in the treatment of generalized anxiety disorder without depression over 8 weeks. Imipramine showed a trend of being significantly better on the primary outcome measure (the Hamilton Anxiety Scale [Ham-A]) and was statistically superior to diazepam on the Psychic Anxiety factor of the Ham-A. Psychic anxiety includes the items of worry, anxious mood, tension, fears, and concentration problems. Diazepam and imipramine had identical endpoint Ham-A Somatic Anxiety factor scores, suggesting that they are equally effective against the somatic anxiety symptoms in generalized anxiety disorder. This suggests that imipramine is a better "anti-worry" medication than the benzodiazepine. Patients taking diazepam had an earlier response than those taking imipramine.

Generally, benzodiazepines are thought to be ineffective in the treatment of OCD.

Benzodiazepines are often prescribed for patients with PTSD. Although benzodiazepines may improve sleep and reduce agitation initially in PTSD, the weight of evidence suggests that in the longer term they are not particularly effective for the core symptoms of this disorder, and more-effective alternatives are preferable (Berger *et al.* 2009; Cifu *et al.* 2013; Guina *et al.* 2015; Jeffreys *et al.* 2012; Spaulding 2012). An added complication is that patients with PTSD have higher rates of DSM-IV (American Psychiatric Association 1994) substance abuse and dependence than the general population, which can further complicate their treatment. For all these reasons, benzodiazepine use in PTSD is discouraged by most clinical practice guidelines (e.g., American Psychiatric Association, British Association for Psychopharmacology, International Consensus Group on Depression and Anxiety, International Society for Traumatic Stress Studies, Veterans Affairs/Department of Defense) (American Psychiatric Association 2004; Baldwin *et al.* 2005; Ballenger *et al.* 2000; Foa *et al.* 2009; U.S. Department of Veterans Affairs and U.S. Department of Defense 2017). The strongest evidence for effective pharmacotherapy in PTSD is for SSRIs. A meta-analysis of medications used to treat PTSD found effect sizes of 0.49 and 1.38 for benzodiazepines and SSRIs, respectively (Van Etten and Taylor 1998).

Studies have compared intramuscular clonazepam against intramuscular haloperidol in the management of acute psychotic agitation. Clonazepam reduced agitation, but haloperidol had a more rapid onset (Chouinard *et al.* 1993). Patients with schizophrenia have high levels of anxiety and frequently experience panic attacks. Overall, it appears that benzodiazepines have a role in the acute management of agitation, and their use can reduce the need for antipsychotics or the dosage of antipsychotics used.

Side Effects and Toxicology

Benzodiazepines are among the safest drugs, but unwanted effects do occur. The first 1,4-benzodiazepines, such as diazepam and flurazepam, had slow rates of elimination and low receptor-binding affinities. Their main side effect was excessive daytime sleepiness. The late 1970s saw the introduction of the 1,4-benzodiazepines flunitrazepam and lorazepam, which had shorter half-lives and were more potent. These drugs were associated with greater efficacy but also with more rapid development of tolerance and significant withdrawal problems. The triazolobenzodiazepines were introduced in the 1980s and were even more potent and had even shorter half-lives. They also have been found to be associated with amnesia, daytime anxiety, early morning insomnia, and withdrawal problems such as rebound insomnia, anxiety, and seizures (Noyes *et al.* 1986). Short-term benzodiazepine use can decrease sleep time, increase rapid eye movement (REM) sleep, decrease slow-wave sleep, increase stage 2 non-REM sleep, and decrease delta wave sleep (Poyares *et al.* 2004; Morin *et al.* 2005). However, many benzodiazepines are approved for and are effective for the treatment of insomnia (Bostwick *et al.* 2012).

Sedation and drowsiness are common, occurring in 4%-9% of patients taking benzodiazepines. Ataxia occurs in up to 2%. The drowsiness tends to disappear with time or a reduction in dosage (Greenblatt *et al.* 1982b; Miller 1973; Svenson and Hamilton 1966). Benzodiazepines may impair psychomotor performance. Shortly after administration at their peak concentration, most benzodiazepines cause anterograde amnesia (Lister *et al.* 1988). These effects depend on potency and route of administration (Bixler *et al.* 1979). Overall, this memory impairment appears to be independent of the degree of sedation produced by the drug (Scharf *et al.* 1988). Benzodiazepine-treated

subjects are often unaware of or underestimate the extent of their memory impairment (Roache and Griffiths 1985, 1987).

Hyperexcitability phenomena such as early morning awakening and rebound anxiety and nervousness are more likely with the short-half-life, high-potency benzodiazepines such as triazolam, alprazolam, lorazepam, and brotizolam (Kales *et al.* 1983, 1986, 1987; Vela-Bueno *et al.* 1983). Treatment-emergent hostility (Rosenbaum *et al.* 1984) may be seen in up to 10% of patients receiving benzodiazepines. Patients may become paradoxically aggressive, destructive, and sexually inappropriate in ways that are out of character on benzodiazepines, especially when combined with alcohol or when taken in dosages that are too high acutely. These complications are usually transient but can cause legal problems for the patient (Lader 1990; Jones *et al.* 2011).

These side effects are most likely to appear early in treatment, are unrelated to pretreatment impulsivity, and have been reported with all benzodiazepines except for oxazepam. Treatment-emergent mania has been reported with alprazolam (Goodman and Charney 1987; Pecknold and Fleury 1986; Strahan *et al.* 1985).

Since the 1960s, benzodiazepines have been found to produce anterograde amnesia, even with oral dosing (Lister 1985). The deficit is one of disrupted consolidation and not impairment of memory retrieval. The degree of amnesia can range from minimal inability to retain isolated pieces of information to total inability to recall any activities that occurred during a specific period. Whether some benzodiazepines are more likely than others to produce amnesia remains an unresolved question.

Cognitive Impairment and Risk of Alzheimer's Disease

Some publications have raised concerns that the long-term use of benzodiazepines may lead to cognitive and other impairments that persist long after the drugs have been discontinued. Abnormal CT scans were reported for long-term users of benzodiazepines in one study (Lader *et al.* 1984) but not in others (Poser *et al.* 1983; Rickels 1985). Busto *et al.* (2000) found no difference in the CT brain scans of patients taking benzodiazepines compared with control subjects. Long-term benzodiazepine users have been compared with control subjects and found to have cognitive impairments that reversed on reexamination after taper (Golombok *et al.* 1988; Lucki *et al.* 1986; Rickels *et al.* 1999; Sakol and Power 1988). Another study found that after long-term use, if the benzodiazepine was stopped, there was only partial recovery even after 6 months (Tata *et al.* 1994).

Billioti de Gage *et al.* (2014) reported inferential evidence suggesting that the use of benzodiazepines for longer than 3 months may be associated with an increased risk of Alzheimer's disease. They used a case-control design to minimize sampling bias and sampled subjects 6 years before the official diagnosis of Alzheimer's disease to control for "reverse bias" (the possibility that Alzheimer's disease resulted in benzodiazepines being used before the onset of the dementia). Salzman and Shader (2015) wrote a rejoinder to this study highlighting its methodological limitations and offering alternative interpretations for the findings. They pointed out that the results "could be interpreted to suggest that benzodiazepine use does not cause increased Alzheimer's disease, but Alzheimer's disease causes an increased need for benzodiazepine treatment in some patients" (p. 2), notably for the prodromal anxiety and insomnia so frequently associated with this illness. In their editorial, Balon *et al.* (2015) urged caution in the interpretation of the results and noted that it was "premature to conclude that benzodiazepines are a causative factor in a multidimensional disorder such as Alzheimer's disease" (Balon *et al.* 2015, p. 244).

Pariente *et al.* (2016) reviewed the literature on the association between benzodiazepine use and the risk of dementia disorders. Nine of the 11 studies reported a harmful effect; 1 study reported a protective effect; and the most recent, largest, best controlled, and most prospectively designed study found no effect. The problem in interpreting a finding of any such association in an inadequately controlled meta-analytic study is that both anxiety and sleep disturbances are common prodromal symptoms in dementia. A lack of adequate controls confounds the interpretation of results in these studies.

A *BMJ* study (Gray *et al.* 2016) followed 3,434 adults ages 65 years and older for 7 years. None had dementia at study initiation; 23% developed dementia by the end of the study. Gray and colleagues used computerized pharmacy data to assess benzodiazepine use. They found no link between the highest level of benzodiazepine use (on average, 1 year of daily use) and dementia or cognitive decline. A small increased risk for dementia was seen in people with moderate (1-4 months) and low (up to 1 month) levels of benzodiazepine use, but not in those using benzodiazepines for longer than 4 months. The authors concluded that the pattern of findings "does not support the theory that cumulative benzodiazepine use at the levels observed in our population is causally related to an increased risk for dementia or cognitive decline" (Gray *et al.* 2016, p. 8). A recent 2020 study of 235,465 Danish adults with affective disorder found no association between benzodiazepine use and later development of dementia. The same study found that lower benzodiazepine use was associated with risk of dementia, but higher benzodiazepine use was not (Osler and Jorgensen 2020).

Practice guidelines recommend that benzodiazepines be avoided in Alzheimer's disease and restricted to short-term, as-needed use by older adults (Madhusoodanan and Bogunovic 2004; Salzman 1990). However, others may agree with the comment by Salzman and Shader (2015), both seasoned and knowledgeable psychopharmacologists, that "experienced geriatric clinicians often find that judicious use of low-dose, short half-life benzodiazepines reduces stress, promotes daytime functioning, and assists in sleep onset; elderly patients themselves report that they would gladly forgo short-term memory reduction in exchange for a calmer daytime and reliable sleep onset" (p. 2).

Drug-Drug Interactions

Antacids may slow the rate of benzodiazepine absorption, but not the extent of absorption (Greenblatt *et al.* 1983a, 1983b). For example, diazepam peak concentrations are 30% lower when antacids are administered concurrently; however, there is no effect on the extent of absorption (e.g., AUC), and the time of peak concentration is delayed by an average of 20-25 minutes (Genentech 2016). An acid medium is needed for conversion of clorazepate to desmethyldiazepam, the active metabolite, which is then absorbed (Shader *et al.* 1978).

In the liver, benzodiazepines are metabolized by oxidation, reduction, or conjugation. Alprazolam, diazepam, clorazepate, prazepam, chlordiazepoxide, bromazepam, and halazepam are metabolized by oxidation; nitrazepam by reduction; and lorazepam, oxazepam, and temazepam by conjugation. Inhibitors of the oxidase system increase the half-life of benzodiazepines that are metabolized by this system. This accentuates the side effects, notably the sedation, ataxia, slurred speech, and imbalance. A decrease in dosage may solve this problem, or a switch to a benzodiazepine that is metabolized by conjugation may be needed.

Monoamine oxidase inhibitors and cimetidine may inhibit oxidative elimination of benzodiazepines (Greenblatt *et al.* 1984).

Oral contraceptives can also inhibit the oxidative system and thereby reduce the clearance and prolong the half-life of benzodiazepines, especially triazolam and alprazolam. Conversely, coadministration of intravenous lorazepam with contraceptive steroids (norethindrone acetate, 1 mg, and ethinyl estradiol, 50 mcg, for at least 6 months) to healthy females ($n = 7$) was associated with a 55% decrease in half-life and a 50% increase in the volume of distribution, resulting in an almost 3.7-fold increase in total clearance of lorazepam in comparison with healthy control females ($n = 8$). In this case, an increase in the lorazepam dosage may be required for patients who are concomitantly taking oral contraceptives (Hospira 2023).

Finally, coadministration of lorazepam (2 mg intravenously) with probenecid (500 mg orally every 6 hours) to 9 healthy volunteers increased lorazepam's half-life by 130% and reduced its total clearance by 45%. No change in volume of distribution was noted during probenecid cotreatment (Hospira 2023). The lorazepam dosage needs to be reduced by 50% when coadministered with probenecid.

A decline in oxidative elimination and clearance occurs with age or liver disease. In older adults, there is a 50% decrease in clearance, with a fourfold to ninefold increase in half-life and a twofold to fourfold increase in the volume of distribution (Peppers 1996). Heparinized patients should have partial thromboplastin time monitored more closely, because it is prolonged by benzodiazepines (Routledge *et al.* 1980). Because antidepressants such as fluoxetine, paroxetine, and nefazodone and protease inhibitors such as indinavir sulfate inhibit the cytochrome P450 enzyme 3A4, they inhibit the metabolism of triazolobenzodiazepines such as midazolam, alprazolam, and triazolam.

The FDA updated and revised the boxed warning on all benzodiazepines in September 2020. This change was driven by concerns over the coadministration of opioids and benzodiazepines. It advised caution when coprescribing benzodiazepines and opioids (U.S. Food and Drug Administration 2020). Nearly 2 million U.S. adults were coprescribed benzodiazepines and opioids between September 2016 and December 2017 (Zhang *et al.* 2019). The U.S. national rate for concomitant use of benzodiazepines and opioids rose from 9.8 to 62.5 per 10,000 outpatient visits between 1993 and 2016 (Hirschtritt *et al.* 2017). For patients taking benzodiazepines, the risk of death from drug overdose increases when they concomitantly take opioids and other CNS depressants. Benzodiazepine-related deaths increased approximately tenfold between 1999 and 2017 (from 0.5 per 100,000 in 1999 to almost 5 per 100,000 in 2017) (VanHouten *et al.* 2019). The FDA boxed warning also reaffirmed the need to warn patients about the risks of benzodiazepines; to assess the risk of abuse, misuse, and addiction for each patient; to prescribe the lowest effective dose for the shortest treatment duration; to taper patients off benzodiazepines slowly; and to conduct frequent follow-up with patients prescribed benzodiazepines (Hirschtritt *et al.* 2021; U.S. Food and Drug Administration 2020).

Clinical Issues

Despite decades of research, the optimal extent and duration of appropriate benzodiazepine use in the treatment of anxiety and related disorders remain unresolved. This is primarily because of concerns expressed by prescribers, regulators, and the public about issues such as tolerance, dependence, and abuse liability of this class of medications.

Tolerance

In a study of persistent users of alprazolam and lorazepam, Romach *et al.* (1995) found that most were not abusing these benzodiazepines, nor were they addicted to them; rather, they were using them appropriately for a chronic disorder and at a constant or a decreasing dosage. Soumerai *et al.* (2003) found no relationship between long-term use of benzodiazepines and escalation to high dosages in 2,440 long-term (at least 2 years) users of benzodiazepines and noted that escalation to a high dosage was very rare.

The cross-tolerance between the benzodiazepines, although good, is not perfect, and it is preferable to switch patients gradually from one benzodiazepine to another and to use comparable doses of each during the switch. One milligram of alprazolam is approximately equivalent to 0.7 mg of clonazepam, 10 mg of diazepam, or 1 mg of lorazepam.

Withdrawal

A withdrawal syndrome is defined as a predictable constellation of signs and symptoms involving altered CNS activity (e.g., tremor, convulsions, or delirium) after the abrupt discontinuation of, or a rapid decrease in, dosing of the drug (Rinaldi *et al.* 1988). Typically, a withdrawal syndrome from short-half-life benzodiazepines will intensify by the second day, will usually have peaked by day 5, and will begin to decrease and taper off by day 10. After 2 weeks, withdrawal symptoms usually have become minimal or are absent. Drug factors associated with withdrawal symptoms include length of use, dosage, potency, and rate of discontinuation. The most common symptoms are anxiety, restlessness, irritability, insomnia, agitation, muscle tension, weakness, aches and pains, blurred vision, and racing heart, in that order (O'Brien 2005). Nausea, sweating, runny nose, hypersensitivity to stimuli, and tremor are less common. Severe withdrawal symptoms, such as psychosis, seizures, hallucinations, paranoid delusions, and persistent tinnitus, are rare and are more likely to occur in abrupt withdrawal from high dosages of high-potency benzodiazepines and in older adults (American Psychiatric Association 1990; Lader 1990; Petursson and Lader 1981).

The minimum duration of use after which clinically significant withdrawal symptoms can be expected has not been definitively determined. At the end of any course of treatment with therapeutic dosages and a duration greater than 3 weeks, withdrawal of the benzodiazepine should be done as a very slow taper. This reduces the risk of unpleasant withdrawal symptoms and the danger of withdrawal seizures and minimizes rebound reactivation of the underlying anxiety disorder (Fontaine *et al.* 1984; Pecknold *et al.* 1988; Power *et al.* 1985).

A follow-up study of 123 benzodiazepine-dependent patients screened for entry into a tapered discontinuation program identified three groups: those who had completed the program (*n* = 48), those who had not (*n* = 38), and those who had undergone no drug tapering (*n* = 37). Among the completers, 73% remained benzodiazepine free at the end of 3 years, compared with 39% of the program noncompleters and 14% of the no-taper group (Rickels *et al.* 1991).

Addiction Potential

In our zeal to heal an anxiety disorder, are we creating a population of addicted patients? Much misinformation and concern are generated because terms such as *addiction* are often used pejoratively and without precise definition. For example, the terms *addiction, physical dependency,* and *withdrawal syndrome* are often used interchangeably. Some presume that a medicine's being associated with a withdrawal syndrome is evidence that the medicine is addictive. Some clinicians believe that benzodiazepines that require frequent dosing during the day are more addictive than those that require less-frequent dosing. In reality, frequency of dosing is a function of the duration of therapeutic action of the drug rather than of any innate addiction potential of the drug.

Most of the literature discussing benzodiazepine dependence liability uses older terminology. *Substance dependence* is defined as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by the presence of three (or more) of seven criteria, occurring at any time in the same 12-month period (American Psychiatric Association 2000). *Addiction,* by contrast, is defined as a chronic disorder associated with compulsive use of a drug, resulting in physical, psychological, or social harm to the user and continued use despite that harm (Rinaldi *et al.* 1988). Addiction involves both intense drug-seeking behavior and difficulty in stopping the drug use. If these criteria are used, benzodiazepines are not addictive drugs. *Physical dependence* is different from addiction and is defined as a physiological state of adaptation to a drug, with the development of tolerance to the drug's effects and the emergence of a withdrawal syndrome during prolonged abstinence. During withdrawal after chronic use, biochemical, physiological, or behavioral problems may be triggered. When used on a regular schedule, benzodiazepines are associated with physical dependence and have a withdrawal syndrome.

In DSM-5 (American Psychiatric Association 2013), the terms *abuse* and *dependence* are no longer used in relation to substances. Instead, DSM-5 uses the more neutral term *substance use disorder* to capture the wider range of disorders previously subsumed under *substance dependence* and *substance abuse.* DSM-5 also uses the terms *substance intoxication* and *substance withdrawal. Substance use disorder* is defined as a problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by the presence of 2 (or more) of either 10 or 11 criteria, occurring within a 12-month period. At this time, no large epidemiological studies have used these new criteria in relation to benzodiazepines.

DSM-IV Substance Abuse

Studies of DSM-IV substance abuse use four criteria for benzodiazepine abuse. A benzodiazepine is being abused if it is used 1) to get high, 2) to promote psychological regression, 3) at dosages higher than prescribed, and 4) after the medical indication has passed (Dietch 1983). Based on this definition, the data suggest that the incidence of benzodiazepine abuse in clinical practice is low.

The incidence of benzodiazepine dependence in the therapeutic setting (among those for whom the drug is medically correctly prescribed) was estimated to be 1 case in 50 million patient-months (Marks 1978). Of these cases, 92% were associated with alcohol or other drugs of abuse. This estimate is probably on the low side because it is based on the number of published cases of dependence from 1961 to 1977.

In Basel, Switzerland, with a catchment area of 300,000 people, physicians were surveyed on the prevalence of benzodiazepine abuse in their patients. Only 31 patients were identified, for a prevalence of 0.01%, or 1 in 10,000. An additional 88 polysubstance abusers were identified (Ladewig and Grossenbacher 1988). In a random sample of all psychiatric hospitalizations over 15 years (1967-1983) in Sweden (*N* = 32,679), Allgulander (1989) found only 38 admissions for substance dependence on sedative-hypnotics. Twenty-one of the 38 patients had polysubstance abuse, and 17 had sedative-hypnotic abuse.

In another study of all medical and psychiatric hospitalizations (*N* = 1.6 million) in Stockholm County, Sweden, Allgulander (1996) found that 0.04% of "prescribed medication" users (including those using benzodiazepines) were ever admitted for medical problems relating to their drug use. In a study of 5,426 U.S. physicians randomly selected from the American Medical Association Physician Masterfile database, Hughes *et al.* (1992) found that although 11.9% had used benzodiazepines in the past year, only 0.6% met DSM-III-R (American Psychiatric Association 1987) criteria for benzodiazepine abuse, and only 0.5% met criteria for benzodiazepine dependence. In 1990, the American Psychiatric Association task force concluded that benzodiazepines were not normally drugs of abuse but noted that people who abused alcohol, cocaine, and opiates were at increased risk for benzodiazepine abuse (Salzman 1991).

A number of studies have noted no increase in dosage with long-term therapy lasting from 1 to 2.5 years, even though many of the patients had residual symptoms that would have benefited from a dosage increase or more intensive or additional treatment strategies (Pollack *et al.* 1986; Sheehan 1987). Nonanxious individuals and those with low anxiety levels reported finding benzodiazepines dysphoric (Reed *et al.* 1965), preferred placebo to diazepam

(Johanson and Uhlenhuth 1978, 1980), or rated their mood as less happy and pleasant after they were given 10 mg of diazepam (Svensson *et al.* 1980).

Although the data suggest that the prevalence of benzodiazepine abuse or dependence is generally low, this is not true among those who abuse alcohol and other drugs. In a study of chronic alcoholic patients who were high consumers of benzodiazepines, 17% got their benzodiazepines from nonmedical sources (Busto *et al.* 1983). In a study of 1,000 admissions to an alcohol treatment unit, 35% of the patients used benzodiazepines, but only 10% of the total sample were considered abusers or misusers (Ashley *et al.* 1978). A study of 427 patients seeking treatment in Toronto, Ontario, who met DSM-III (American Psychiatric Association 1980) criteria for alcohol abuse or dependence found that 40% were recent benzodiazepine users, and 20% had a lifetime history of benzodiazepine abuse or dependence. By contrast, only 5% of 108 alcoholic patients treated for a year with benzodiazepines for anxiety and tension showed evidence of abuse, and 94% believed that the medication helped them function and remain out of the hospital (Rothstein *et al.* 1976).

Benzodiazepines were the primary drug of abuse for one-third of polydrug abusers (Busto *et al.* 1986), 29% of 113 drug abusers admitting to the street purchase of diazepam in the previous month (Woody *et al.* 1975b), and 40% of patients at a methadone maintenance clinic (Woody *et al.* 1975a). The principal reasons for benzodiazepine use among drug-addicted patients are self-treatment of withdrawal symptoms, relief from rebound dysphoria, or potentiation of alcohol or street drug effects (Perera *et al.* 1987). In one study at an addiction treatment center, 100% of urine samples tested were positive for benzodiazepines, and 44% were positive for multiple nonprescribed benzodiazepines (Iguchi *et al.* 1993). A survey of patients at three different methadone maintenance clinics found that 78%-94% admitted to a lifetime use of benzodiazepines, and 44%-66% admitted to use in the prior 6 months. Snorting of benzodiazepines by people addicted to cocaine has been reported (Sheehan *et al.* 1991), primarily as a means of blunting the anxiogenic effect of cocaine and allowing for a more pleasant and "less edgy" high from that drug. Overall, the existing evidence suggests that benzodiazepine abuse is uncommon, except among people who abuse alcohol or other drugs. There was no significant increase in benzodiazepine dosage in a 2-year follow-up of either 113 "incident" or 992 "prevalent" users of benzodiazepines who had used benzodiazepines for at least 6 months (Willems *et al.* 2013).

Benzodiazepine misuse among adolescents is a growing concern. In a 2018 study of approximately 29,600 U.S. high school students (10th to 12th grade), 3.9% reported use of benzodiazepines (Johnston *et al.* 2019).

Despite extensive data and discussion on this topic, the issue remains and will continue to be controversial, with strong opinions held by opposing camps. Klerman characterized these camps as "pharmacological Calvinism" and "psychotropic hedonism" (Klerman 1972; Rosenbaum 2005). The middle ground suggests that we should not hesitate to prescribe benzodiazepines when it is reasonable, but we should exercise restraint in using them when we see any evidence of substance misuse or abuse (Pomeranz 2007).

Medicolegal Issues

In addition to the issues of dependence and withdrawal described in the previous section, use of benzodiazepines is associated with several potential medicolegal pitfalls. These include issues of teratogenicity, injury, and interaction with substances.

Benzodiazepine Use in Pregnancy and Lactation

Because anxiety disorders have their highest incidence in women during their childbearing years, the clinician may have to advise patients who are planning a pregnancy or who become pregnant while taking a benzodiazepine.

First and Second Trimesters

An important concern in the first and second trimesters is the possibility of teratogenic effects. Diazepam and desmethyldiazepam cross the placental barrier easily, and concentrations are higher in fetal blood than in maternal blood (Idanpaan-Heikkila *et al.* 1971). Early concern over benzodiazepine exposure in pregnancy arose because benzodiazepines

act on GABA receptors, and GABA is involved in palate shelf reorientation (Wee and Zimmerman 1983; Zimmerman and Wee 1984). The teratogenic effects of benzodiazepines are a matter of controversy, however. Exposure to benzodiazepines has been associated with teratogenic effects, including facial clefts and skeletal anomalies in newborns in some animal studies (Miller and Becker 1975; Walker and Patterson 1974; Wee and Zimmerman 1983; Zimmerman 1984; Zimmerman and Wee 1984) but not in others (Beall 1972; Chesley *et al.* 1991). Early studies in humans, including retrospective and case-control studies, reported an increased risk of oral clefts associated with diazepam (Aarskog 1975; Livezey *et al.* 1986; Safra and Oakley 1975; Saxen 1975; Saxen and Lahti 1974). However, these results have been criticized on methodological grounds and are contradicted by more recent prospective studies, case-control studies, and meta-analyses that show no increased risk of oral clefts related to benzodiazepine use in pregnancy (Altshuler *et al.* 1996; Bracken 1986; Czeizel 1987-1988; Dolovich *et al.* 1998; Ornoy *et al.* 1998; Pastuszak *et al.* 1996; Rosenberg *et al.* 1983; Shiono and Mills 1984).

Pooled data from seven cohort studies do not support an association between fetal exposure to benzodiazepines and major malformations (Dolovich *et al.* 1998).

Third Trimester and Labor

Two concerns associated with benzodiazepine use in the last trimester and through delivery are the possibilities of CNS depression and a withdrawal syndrome in the neonate. Signs of CNS depression may include hypotonia, lethargy, sucking difficulties, decreased fetal movements, loss of cardiac beat-to-beat variability, respiratory depression, and thermogenesis. These symptoms in the neonate are more likely with higher dosages and longer duration of benzodiazepine use by the mother. There have been numerous reports of "floppy infant syndrome" in babies born to women taking diazepam long term during pregnancy (Gillberg 1977; Haram 1977; Rowlatt 1978; Speight 1977). Neonatal withdrawal symptoms may include hyperactivity and irritability. The occurrence of neonatal withdrawal symptoms is well documented (Barry and St Clair 1987; Briggs *et al.* 1998; Cree *et al.* 1973; Fisher *et al.* 1985; Gillberg 1977; Haram 1977). Symptoms may be present at birth or appear weeks later and may continue for a period of time (Schardein 1993).

Diazepam in isolated doses is safe during labor (Briggs *et al.* 1998). There are conflicting reports on the effect of benzodiazepines on Apgar scores. Lowered Apgar scores have been reported with benzodiazepine use in some studies (Berdowitz *et al.* 1981; McElhatton 1994). One study found that diazepam reduced Apgar scores only when doses greater than 30 mg were administered during labor (Cree *et al.* 1973).

Breastfeeding

Neonates have limited capacity to metabolize diazepam (Morselli *et al.* 1973). Benzodiazepines are excreted in breast milk (Llewellyn and Stowe 1998). Because of the neonate's limited capacity to metabolize these drugs, they can accumulate and cause sedation, lethargy, and weight loss in the nursing infant. Although the extent to which benzodiazepines actually accumulate in the serum of breastfeeding infants is a matter of debate (Birnbaum *et al.* 1999), and three decades of studies support a low incidence of toxicity and adverse effects (Birnbaum *et al.* 1999; Llewellyn and Stowe 1998), caution regarding use of benzodiazepines while breastfeeding is advised.

Benzodiazepines and Risk of Accidental Injury

Another area of risk of benzodiazepine use relates to issues of psychomotor impairment resulting in injury. An examination of the medical records of a group of benzodiazepine users and nonusers found that the benzodiazepine users were more likely than nonusers to experience at least one episode of accident-related health care, to have a greater number of accident-related inpatient days, and to use significantly more non-accident-related health care services. Accident-related use of health care was most likely in the first month after the drug was prescribed (Oster *et al.* 1987). For older adults, the issue of benzodiazepine use increasing the risk for falls and fractures is of great concern because hip fractures are associated with increased morbidity and mortality. A number of studies (Boston Collaborative Drug Surveillance Program 1973; Cummings *et al.* 1995; Greenblatt *et al.* 1977; Hemmelgarn *et al.* 1997; Ray *et al.* 1992; Roth *et al.* 1980) have found a greater risk for falls with the use of long-half-life benzodiazepines, and others (Cumming and Klineberg 1993; Herings *et al.* 1995; Leipzig *et al.* 1999) have found the risk to be greater with short-half-life drugs. A more recent study (Wang *et al.* 2001) found the risk for hip fracture in older adults to be the same with the use of short-or long-half-life benzodiazepines. The researchers did find that the risk increased when benzodiazepine dosages were greater than 3 mg/day in diazepam equivalents. They also found the greatest risk to occur shortly after initiation of therapy and after 1 month of continuous use. A 5-year prospective cohort study following a large group of older adults newly exposed to benzodiazepines found that the risk of injury varied by benzodiazepine, independent of half-life, as did the risk associated with increasing dosage for individual agents (Tamblyn *et al.* 2005). Older adults using benzodiazepines were at greatest risk for a motor vehicle accident (Hemmelgarn *et al.* 1997). On the other hand, a study of the effect of New York State requiring triplicate forms for prescribing benzodiazepines showed that despite a 50% decrease in the number of prescriptions written, no significant change was seen in age-adjusted risk for hip fractures (Wagner *et al.* 2007).

Patients using benzodiazepines are nearly five times more likely than nonusers to experience a serious motor vehicle accident (Skegg *et al.* 1979). In the first 2 weeks after patients start to use benzodiazepines, there is a several-fold greater risk for hospitalization related to accidental injury compared with patients beginning to use antidepressants or antipsychotics (Neutel 1995).

The best protection from benzodiazepine-related injury is a discussion of these issues with patients before a benzodiazepine is prescribed. This discussion, including cautionary statements about driving or operating dangerous machinery, should be documented in the chart at the start of therapy. Patients should be educated about potentiation by alcohol or other sedating drugs. They also should be strongly advised never to abruptly discontinue the medicine because of a risk of seizures (Noyes *et al.* 1986), and the clinician's communication of this advice should be documented. Prescribing benzodiazepines for patients with a current or lifetime history of a substance use disorder should be done infrequently and only after a risk-benefit discussion is documented in the chart. It is good practice to routinely screen all patient for substance use disorders before prescribing a benzodiazepine and to document that this was done.

Benzodiazepine Use During the Coronavirus Disease 2019 (COVID-19) Pandemic

The COVID-19 pandemic was declared a national emergency in the United States on March 13, 2020. COVID-19 was linked to an increase in mental health problems, drug overdoses, and abuse of alcohol and controlled and illicit y (see

Holland *et al.* 2021 and de Dios *et al.* 2021). de Dios *et al.* (2021) studied the effect of the COVID-19 pandemic on the prescription-filling patterns for benzodiazepines and opioid drugs across 38 states from January 2019 to December 2020. When de Dios and colleagues compared the prescription patterns in the months before the pandemic declaration date (March 13, 2020) with those after that date, they found a statistically significant 2.0% increase in the proportion of all filled prescriptions for controlled substances that were benzodiazepine prescriptions and a 1.7% decrease in the proportion that were opioid prescriptions. Only the opioid prescription rate returned to predeclaration levels after May 18, 2020 (Milani *et al.* 2021). This report of an increase in benzodiazepine prescriptions is consistent with the findings of Jones *et al.* (2021), who reported that prescription rates returned to forecasted patterns in April-May 2020.

In a study of the records of approximately 15-17 million adults from 2018 through March 2021, Milani *et al.* (2021) found that the benzodiazepine prescription rate for women decreased 0.03% monthly from 2018 to January 2020, increased 0.06% monthly from January 2020 to April 2020, and then decreased 0.04% monthly from April 2020 to March 2021. For men there were no statistically significant changes in the slope of rates of benzodiazepine prescription over those same time periods. For individuals ages 65 years and older, the pattern was similar to that noted for women (Milani *et al.* 2021).

Conclusion

If given in adequate dosages, benzodiazepines are effective in the treatment of anxiety. They have a lower mortality and morbidity per million prescriptions than some of the alternatives (Girdwood 1974), including atypical antipsychotics. Benzodiazepines are quicker in onset of action, easier for the clinician to use, associated with better compliance, and less subjectively disruptive for the patient than any of the other medication alternatives. Until benzodiazepines are replaced by another class of medicine that is safer, better tolerated, and as rapidly effective, it is likely that they will continue to be prescribed to a significant proportion of patients.

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CHAPTER 23

Buspirone

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Altered central serotonergic function is implicated in several psychiatric disorders, especially mood and anxiety disorders. Discovery of the serotonin type 1A (5-HT_{1A}) receptor linked modulation of serotonin (5-hydroxytryptamine [5-HT]) neurotransmission to anxiety symptoms.

The notion of a role for serotonin in the treatment of anxiety arose from the finding that benzodiazepines reduce brain 5-HT turnover and that para-chlorophenylalanine (pCPA), an inhibitor of serotonin synthesis, mimics the effects of benzodiazepines in behavioral models of anxiety (Wise *et al.* 1972). Discovery of the 5-HT_{1A} receptor partial agonist buspirone confirmed that serotonin plays a key role in anxiolysis (Eison and Eison 1994). Because both benzodiazepines and buspirone reduce 5-HT impulse flow, albeit by different mechanisms, altered serotonergic tone was postulated to be an underlying factor in the etiology of anxiety disorders.

The 5-HT_{1A} Receptor

Identification of multiple serotonin receptors (Hoyer *et al.* 2002; Pierce *et al.* 2002) and discovery of the role of the 5-HT_{1A} receptor, which couples negatively to adenylyl cyclase (De Vivo and Maayani 1986; Savitz *et al.* 2009), led to pharmacological characterization of this receptor through the use of selective agonists (Hamon *et al.* 1984); selective partial agonist azapirones, such as buspirone (Figure 23-1); and specific antagonists (Fletcher *et al.* 1996). Clinical development of 5-HT$_{1A}$ partial agonists, which were active in models of both anxiety and depression, ensued when it became apparent that this receptor plays a central role in neuropsychiatric disorders (Robinson *et al.* 1989a).

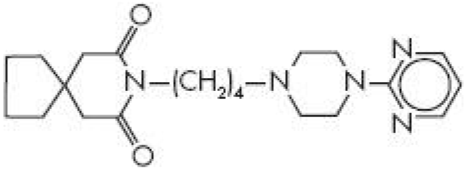

FIGURE 23-1. Chemical structure of buspirone.

Pharmacological and Clinical Implications

High regional density of 5-HT$_{1A}$ receptors in midbrain, hippocampus, and limbic areas comports with the notion that 5-HT neurotransmission modulates mood and anxiety. Brain regions with high densities of 5-HT$_{1A}$ receptors control thermoregulation, endocrine function, appetite, aggressive and sexual behavior, and mood. Mice lacking the 5-HT$_{1A}$ receptor gene exhibit anxious behavior (Parks *et al.* 1998; Pattij *et al.* 2002).

5-HT$_{1A}$ receptors on 5-HT neurons in midbrain raphe regions modulate release of 5-HT at synapses in forebrain. These somatodendritic autoreceptors control synthesis and impulse flow (Yocca 1990) and release (Sharp *et al.* 1989) of neurotransmitters from ascending 5-HT-containing neurons. Using the receptor-specific, tritiated ligand 8-hydroxy-2-[*N*-dipropylamino]-tetralin (8-OH-DPAT), Stockmeier *et al.* (1998) reported increased binding of the ligand to inhibitory 5-HT$_{1A}$ autoreceptors in the dorsal raphe of suicide victims, in support of the hypothesis that these people had diminished 5-HT neuronal activity. Imaging studies of brain regions using 8-OH-DPAT or the receptor-specific radioligand [carbonyl-

^{11}C]WAY-100635 confirmed diminished function (reduced binding potential) of serotonin 5-HT$_{1A}$ receptors in the brains of both suicide victims and patients with major depressive disorder (MDD) compared with matched control subjects (Boldrini *et al.* 2008; Drevets *et al.* 2007; Hirvonen *et al.* 2008; Meltzer *et al.* 2004), indicating diminished activity of 5-HT neurons in mood disorders. Blunted 5-HT$_{1A}$ receptor-mediated response to corticosteroids is present in patients with MDD, suggesting desensitization of these receptors in patients with anxiety and depression (Lesch 1992; Rausch *et al.* 2006; Stahl 1992).

5-HT Receptors and Partial Agonists

Given the evidence implicating 5-HT in mood disorders and the role of the 5-HT$_{1A}$ receptor in 5-HT neurotransmission, drugs targeting this receptor hold interest for the treatment of mood and anxiety disorders. Partial agonists of this receptor act in part by signal attenuation at one or more target receptors (Yocca and Altar 2006). The partial agonist buspirone produces a therapeutic response with an excellent safety profile and was developed for the treatment of anxiety and associated depression.

The selective 5-HT$_{1A}$ receptor partial agonist gepirone received FDA approval for the treatment of MDD in 2016 but only very recently (2023) reached the market for that indication. Gepirone extended-release (ER) has also been shown to have anxiolytic properties (Kaur Gill *et al.* 2019; Pecknold *et al.* 1993) and is in Phase III trials for generalized anxiety disorder (GAD) and hypoactive sexual desire disorder (FabreKramer Pharmaceuticals 2023). Other azapirones include tandospirone, ipsapirone, and lesopitron. There has been one completed trial of tandospirone in GAD, but there are currently no published findings.

History and Development

Buspirone hydrochloride, an azaspirodecanedione derivative (Wu *et al.* 1969), is a dopamine autoreceptor and D$_3$ receptor antagonist and partial agonist at 5-HT_{1A} receptors. It was originally studied as a putative antipsychotic agent but was not efficacious (Sathananthan *et al.* 1975). Until subsequent discovery of buspirone's high-affinity binding to the newly discovered 5-HT_{1A} receptor, the anxiolytic activity of buspirone was presumed to be dopaminergic.

A Phase II proof-of-concept study of patients with DSM-II (American Psychiatric Association 1968) anxiety disorder showed significant anxiolytic efficacy of buspirone compared with placebo (Goldberg and Finnerty 1979), which fostered its clinical development as an antianxiety agent (Robinson 1991). Later, buspirone was found to bind to dopamine D_3 and D_4 receptors, suggesting its possible utility in the treatment of drug addiction (Bergman *et al.* 2013; Le Foll and Boileau 2013).

Pharmacological Profile

Buspirone has low affinity in vitro for noradrenergic, cholinergic, and histaminergic receptors, and it does not displace [^{3}H] diazepam or [^{3}H] nitrazepam from the benzodiazepine receptor complex (Riblet *et al.* 1982). Although buspirone displaces [^{3}H] spiperone from rat striatal membranes at high concentrations (Mennini *et al.* 1986, 1987), dopamine receptor binding appears to play no role in either the therapeutic effects or the side effects of buspirone (Eison *et al.* 1991). In the frontal cortex of freely moving rats, buspirone produces dose-dependent decreases in dialysate levels of 5-HT and increases in levels of dopamine and norepinephrine, findings indicative of multiple mechanisms by which buspirone may modify monoaminergic neurotransmission (Gobert *et al.* 1999).

The discovery that nanomolar quantities of buspirone displaced [^{3}H]5-HT from hippocampal membranes (Glaser and Traber 1983) led to elucidation of buspirone's actions on specific central 5-HT receptors. Buspirone inhibits [^{3}H]5-HT binding to cortical and hippocampal membranes (Skolnick *et al.* 1985) and selectively displaces [^{3}H]8-OH-DPAT from 5-HT_{1A} receptor-binding sites in rat hippocampal membranes with high affinity (24 nM) (Yocca 1990).

The antianxiety properties of buspirone reflect its actions at both presynaptic and postsynaptic 5-HT_{1A} receptors (Eison and Eison 1994; Yocca 1990). At presynaptic 5-HT_{1A} receptors in the dorsal raphe, buspirone acts as a full agonist, inhibiting neuronal 5-HT synthesis and firing, whereas at postsynaptic receptors in hippocampus and cortex it functions as a partial agonist.

Buspirone differs from benzodiazepines in that it does not inhibit motor coordination or spontaneous motor activity but can produce serotonin syndrome in rats (Barrett and Witkin 1991; Eison *et al.* 1991). Unlike benzodiazepines, buspirone lacks abuse potential and does not impair psychomotor performance alone or in combination with ethanol (Griffith *et al.* 1986; Smiley 1987; Sussman and Chow 1988). The behavioral effects of buspirone and benzodiazepines differ somewhat in animal models of anxiety (Barrett and Witkin 1991) in that buspirone does not uniformly increase punished or conflict responding in rats and monkeys. In pigeons, by contrast, buspirone

increases punished response equivalently to benzodiazepines, a characteristic of 5-HT_{1A} receptor agonists such as 8-OH-DPAT, whereas tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), opioids, antipsychotics, and psychomotor stimulants do not. Like benzodiazepines, buspirone increases exploratory and social interaction behavior in rodents. It also has been shown to decrease the exaggerated freezing response in a mouse model of PTSD-like symptoms (Malikowska-Racia *et al.* 2020).

5-HT_{1A} agonists are active in animal models of depression. Similar to tricyclic antidepressants and SSRIs, 5-HT_{1A} agonists such as 8-OH-DPAT and the azapirones produce antidepressant-like behavior in the forced-swim test in rats (Wieland and Lucki 1990). This effect occurs in the absence of changes in locomotor activity and is not diminished by pretreatment with the 5-HT synthesis inhibitor pCPA, suggesting that 5-HT_{1A} agonists produce an antidepressant response through postsynaptic effects on 5-HT_{1A} receptors. Buspirone's activity in preclinical models of depression comports with findings in placebo-controlled trials of buspirone indicative of its antidepressant properties (Rickels *et al.* 1991; Robinson *et al.* 1989a). The buspirone metabolite 1-(2-pyrimidinyl)piperazine (1-PP) lacks such activity.

Pharmacokinetics and Mechanism of Action

With oral administration, buspirone undergoes extensive first-pass metabolism by cytochrome P450 3A4 enzymes, with a mean elimination half-life of 3-4 hours (Gammans and Johnston 1991). Food prolongs the elimination half-life of buspirone, as does hepatic or renal impairment. The pharmacokinetics of buspirone in older adults and young adults do not differ (Gammans *et al.* 1989).

Buspirone has several metabolites with differing pharmacological activity: 6-hydroxybuspirone (6-OH-Bu), 5-hydroxybuspirone, 8-hydroxybuspirone, and 1-PP. Noradrenergic properties of 1-PP may induce unwanted side effects in patients who have panic attacks or are undergoing benzodiazepine withdrawal. Conversion of buspirone to 6-OH-Bu is the major metabolic pathway in the hepatic clearance of buspirone (Dockens *et al.* 2006; Zhu *et al.* 2005), and bioavailability of 6-OH-Bu is greater than that of the parent drug (19% vs. 1.4% for buspirone [Wong *et al.* 2007]), significantly contributing to buspirone's therapeutic activity (Dockens *et al.* 2006). In vitro, 6-OH-Bu exhibits high affinity (25 nM) and partial agonist activity for the 5-HT_{1A} receptor (Wong *et al.* 2007).

The anxiolytic effects of buspirone appear to be mediated by its actions on 5-HT receptors in the limbic system (Eison and Eison 1994; Yocca 1990). In addition to being a 5-HT_{1A} agonist, buspirone acts as both a D_2 agonist and a D_2 antagonist in the anterior pituitary, regulating prolactin levels. Buspirone has significant neuroendocrine effects beyond those related to dopamine receptors. 5-HT_{1A} receptors regulate the neuroendocrine hormones, including growth hormone, adrenocorticotropic hormone, corticosterone, and oxytocin (Gilbert *et al.* 1988; Pan and Gilbert 1992; Van de Kar *et al.* 1985; Vicentic *et al.* 1998). Buspirone produces dose-dependent increases in rat plasma prolactin levels (Meltzer and

Fleming 1982). Buspirone antagonizes the inhibitory effects of dopamine on prolactin release from the rat pituitary gland in vitro, illustrative of its partial agonist activity at D_2 receptors (Meltzer *et al.* 1991). All azapirones decrease body temperature (Cowen *et al.* 1990; Meltzer *et al.* 1991). Buspirone stimulation of prolactin and corticosterone secretion in the rat is increased by pCPA, whereas spiperone inhibits buspirone-induced increases in corticosterone secretion (Meltzer *et al.* 1991). Pindolol, a 5-HT_{1A} antagonist, does not block the buspirone-induced increase in prolactin (Meltzer *et al.* 1991). The neuroendocrine effects of buspirone are complex, reflecting properties of both dopamine antagonism and 5-HT_{1A} partial agonism.

Indications and Efficacy

Approved Clinical Indications

Generalized Anxiety Disorder

Clinical development of buspirone began after positive findings were reported in a placebo-controlled proof-of-concept study of anxious patients (Goldberg and Finnerty 1979). In Phase III placebo-controlled trials comparing buspirone and diazepam, the two anxiolytics had comparable efficacy for patients meeting diagnostic criteria for DSM-II anxiety neurosis (Bohm *et al.* 1990a; Goldberg and Finnerty 1982; Rickels *et al.* 1982). Currently, buspirone is FDA approved for the short-and long-term treatment of GAD and short-term symptomatic relief of anxiety.

Buspirone has a slower onset of therapeutic effect than the benzodiazepines (Enkelmann 1991; Pecknold *et al.* 1989; Rickels 1990). This slower onset is attributable to differences between buspirone and benzodiazepines in relief of somatic anxiety, whereas the two drugs are similar in rates of alleviation of psychic anxiety. Lack of sedation with buspirone also contributes to the perception of a more gradual onset of anxiolysis, similar to that with imipramine (Rickels *et al.* 1993) and SSRIs (Rickels *et al.* 2003). With buspirone, relief of somatic anxiety (particularly insomnia) occurs only after psychic anxiety symptoms abate, whereas the immediate sedating properties of benzodiazepines give the perception of a faster onset of therapeutic benefit.

A 6-month double-blind comparative trial of buspirone and benzodiazepines confirmed that onset of anxiolytic effects was slower with buspirone than with clorazepate during the first 4 weeks of treatment (Rickels *et al.* 1988). With ongoing treatment, however, the therapeutic response to the two drugs was equivalent. Clinical improvement was maintained over the 6-month study period, and therapeutic tolerance did not develop with either drug. On double-blind termination of treatment at 6 months, several patients who stopped clorazepate abruptly experienced relapse, whereas none relapsed in the buspirone group. The finding that symptom relapse did not occur with abrupt discontinuation of buspirone confirmed conclusions from other investigators (Fontaine *et al.* 1984; Noyes *et al.* 1988) that the rapid return of symptoms after discontinuation of clorazepate was attributable to benzodiazepine withdrawal rather than to a recrudescence of the underlying anxiety disorder.

A benzodiazepine may be indicated as initial therapy for chronically anxious patients; however, longer-term benzodiazepine treatment can lead to physical dependence. Benzodiazepine treatment may be inappropriate for some patients because of the risk of substance abuse or cognitive impairment. When a patient is starting buspirone treatment, one should inform the patient that the drug is less sedating and has a

gradual onset of action. Patients can be reassured that buspirone lacks physical dependence potential and does not impair cognition or acquisition of coping skills (Rickels and Schweizer 1990).

Possible clinical benefits of buspirone in benzodiazepine withdrawal syndrome were assessed in 15 patients with chronic anxiety who had previously attempted both abrupt and gradual withdrawal of benzodiazepine treatment without success (Schweizer and Rickels 1986). In this study, addition of buspirone overlapping with tapering of the benzodiazepine dosage did not ameliorate the symptoms of benzodiazepine withdrawal, and no patient could be maintained on buspirone monotherapy after complete withdrawal of benzodiazepine treatment. In other studies, buspirone showed only modest beneficial effects on benzodiazepine withdrawal syndrome (Delle Chiaie *et al.* 1995; DeMartinis *et al.* 2000; Udelman and Udelman 1990).

After buspirone's approval by the FDA, several well-controlled efficacy trials in GAD confirmed the drug's significant anxiolytic efficacy (Enkelmann 1991; Laakmann *et al.* 1998; Lader and Scotto 1998; Murphy *et al.* 1989; Pecknold *et al.* 1989; Scheibe 1996). In a 3-week placebo-controlled comparison trial of 60 patients with anxiety disorder in a general medical setting, Bohm *et al.* (1990a) found buspirone and the benzodiazepine clobazam to be equally effective and superior to placebo in relieving anxiety.

Long-term follow-up at 40 months of patients who previously completed a 6-month controlled trial comparing buspirone and clorazepate revealed that none of the buspirone-treated patients needed anxiolytic medication, whereas more than 50% of the patients treated with clorazepate needed continuation anxiolytic therapy (Rickels and Schweizer 1990).

Case studies support the efficacy of buspirone in treating anxiety in genetic disorders. GAD responded to buspirone in three cases of young adults with Williams's syndrome (Thom *et al.* 2020). Another series of three case studies found a decrease in behaviors attributed to anxiety with buspirone in the neurogenetic disorder Angelman's syndrome (Balaj *et al.* 2019). In all six cases, buspirone was well tolerated and produced sustained response.

Buspirone was not found beneficial in anxiety associated with chemotherapy. In a randomized, placebo-controlled trial of 432 patients, no significant reduction in dyspnea or anxiety in patients with cancer was found (Peoples *et al.* 2016).

Strawn *et al.* (2018) conducted a review and Bayesian analysis of abandoned randomized controlled trials (RCTs) assessing buspirone in youths with anxiety. They found buspirone treatment to be well tolerated in pediatric patients with GAD, although two RCTs were underpowered to detect small effect sizes (Cohen's $d < 0.15$). Strawn and colleagues proposed that Bayesian approaches may facilitate reexamination of data from abandoned clinical trials.

Buspirone was evaluated in older adults with anxiety symptoms in a double-blind, placebo-controlled trial and was found to be both safe and effective (Bohm *et al.* 1990b). Buspirone's lack of sedation and sparing of cognition and memory were strong therapeutic advantages for this population. Meta-analyses of several multicenter trials of buspirone in older adults also showed buspirone to be safe and well tolerated (Ritchie and Cox 1993; Robinson *et al.* 1988).

Buspirone treatment also was assessed in patients with panic disorder in placebo-controlled trials (Pohl *et al.* 1989; Sheehan *et al.* 1990). Buspirone does not diminish

panic attacks. However, a meta-analysis of double-blind three-arm multicenter trials in panic disorder comparing buspirone, imipramine, and placebo found that both imipramine and buspirone reduced anxiety symptoms (Robinson *et al.* 1989b). Buspirone's lack of effect on the number of panic attacks is unsurprising in light of preclinical evidence that buspirone increases firing rates in the locus coeruleus (Eison and Temple 1986) and causes noradrenergic hyperactivity (Sanghera *et al.* 1982), both manifestations of panic disorder.

Mixed Anxiety-Depression

In initial trials of patients with anxiety disorder and subsyndromal depression, depressive symptoms decreased significantly with buspirone treatment (Feighner *et al.* 1982; Goldberg and Finnerty 1979). This finding fostered interest in the potential antidepressant properties of buspirone because of the high comorbidity of GAD and MDD (Brown and Barlow 1992) and led to speculation that GAD and MDD may be differing clinical manifestations of a single underlying diathesis. Genetic studies of patients with MDD and GAD suggested that genetic vulnerability for the two disorders is largely shared (Kendler *et al.* 1992). The relationship between

MDD and GAD and its implications for their clinical treatment have been reviewed (Kendler *et al.* 1992; Roy-Byrne 2008).

Buspirone treatment of patients with MDD associated with significant anxiety symptoms was assessed in placebo-controlled trials (Rickels *et al.* 1991; Robinson *et al.* 1989a, 1990). Patients with MDD were eligible for inclusion in these studies if their Hamilton Rating Scale for Depression (Hamilton 1960) and Hamilton Anxiety Scale (Hamilton 1959) scores were [?] 18 and [?] 15, respectively. The daily dosage ranged up to a maximum of buspirone 90 mg/day (mean [?] 50 mg/day). Buspirone treatment was superior to placebo, with a global response rate (based on Clinical Global Impression-Improvement scale scores) of 70% for buspirone and 35% for placebo (Rickels *et al.* 1991). In a subsequent placebo-controlled study involving 177 geriatric depressed outpatients, Schweizer *et al.* (1998) compared buspirone and imipramine treatment for 8 weeks. There was a statistically significant treatment effect for both buspirone (mean daily dosage [?] 50 mg) and imipramine (mean daily dosage [?] 90 mg) compared with placebo treatment.

Buspirone augmentation of SSRI treatment of partially responding depressed patients leads to further improvement (Dimitriou and Dimitriou 1998; Jacobsen 1991; Landen *et al.* 1998). These findings were confirmed in a report of the Sequenced Treatment Alternatives to Relieve Depression program. Patients who initially did not respond to an adequate therapeutic trial with an SSRI responded when their medication was augmented with either buspirone or bupropion (Trivedi *et al.* 2006). In an exploratory double-blind, placebo-controlled study of patients with an MDD diagnosis, Fava *et al.* (2012) reported significant antidepressant efficacy for combined buspirone 15 mg and melatonin slow release 3 mg. This preliminary finding is mentioned only to indicate ongoing interest in buspirone as a potential augmenter of other antidepressants, not as a treatment recommendation.

Nonapproved Clinical Indications

Potential clinical indications for buspirone treatment unapproved by the FDA were reviewed by Rickels *et al.* (2003); selected studies are mentioned here.

Gastrointestinal Related Disorders

An RCT found buspirone ineffective for patients with functional dysphagia and ineffective esophageal motility compared with placebo (Aggarwal *et al.* 2018). Case studies reported by Caviglia *et al.* (2017) found that patients with functional dyspepsia who did not respond to first-line therapy and reported meal-related discomfort may benefit from buspirone or amitriptyline-based therapies. A single case study of a 14-year-old found efficacy for buspirone in avoidant/restrictive food intake secondary to fear of emesis (Okereke 2018).

Substance-Related Disorders

Several placebo-controlled trials have demonstrated the usefulness of buspirone in facilitating smoking cessation (Hilleman *et al.* 1992; West *et al.* 1991), although its main effect was in smokers who were also highly anxious (Cinciripini *et al.* 1995).

Buspirone has been assessed in several double-blind, placebo-controlled trials involving anxious outpatients with coexisting alcohol use disorder and found to be efficacious (Rickels *et al.* 2003). Buspirone's lack of abuse potential and negligible additive effects on psychomotor and cognitive functions when coadministered with alcohol (Mattila *et al.* 1982) make it a useful addition to pharmacotherapies for alcohol-related disorders.

Buspirone was found to ameliorate symptoms of opioid withdrawal in a placebo-controlled trial (Buydens-Branchey *et al.* 2005). A subsequent study used an animal model investigating morphine reward. Coadministration of buspirone prevented the rewarding effects of morphine and its effects on the metabolism of dopamine and serotonin in the nucleus accumbens and caudate nucleus in rat striatum. The authors suggested that 5-HT$_{1A}$ receptor-dependent modulation of dopamine neurotransmission in the caudate nucleus and nucleus accumbens is involved in modulation of the rewarding effects of morphine in buspirone cotreated animals, documenting an important role of 5-HT$_{1A}$ receptors in drug addiction (Haleem *et al.* 2018).

Although elevations in synaptic dopamine levels have been demonstrated to play a pivotal role in the reinforcing effects of cocaine, neither D_1 nor D_2 receptor antagonists have proved clinically effective in cocaine addiction. Speculating that dopamine D_3 and D_4 receptors might be possible targets for pharmacotherapy, Bergman *et al.* (2013) undertook an investigation of buspirone, which has been found to bind with high affinity to these receptors, to evaluate its functional effects in animal models. On the basis of their finding that buspirone produced a downward shift in the dose-effect function for cocaine-maintained behavior, Bergman *et al.* proposed that buspirone be evaluated for its utility in the management of cocaine addiction. However, in a 16-week double-blind multicenter pilot trial, Winhusen *et al.* (2014) found that buspirone at dosages titrated up to 60 mg/day was not beneficial in preventing relapse to cocaine use. An RCT found buspirone was not effective in intranasal methamphetamine use disorder (Reynolds *et al.* 2017). Another study found buspirone exerts inhibitory effects on psilocybin-induced effects, presumably via 5-HT_{1A} receptor activation, an interaction between 5-HT_{1A} and 5-HT_{2A} receptors, or both (Pokorny *et al.* 2016).

In a related application, an animal model study found that effects of morphine plus buspirone and baclofen plus buspirone had an additive effect on decreasing schedule-controlled response, suggesting a role for buspirone as an augmenting agent in

pain control. Effects of the two combinations produced synergistic thermal antinociception. Naltrexone and CGP35348 antagonized the effects of morphine and baclofen, respectively (Wilkerson *et al.* 2019).

Adjunctive Use in Schizophrenia

Several studies have evaluated the adjunctive use of buspirone in patients with chronic schizophrenia being treated with typical and atypical antipsychotic drugs. In a 6-month placebo-controlled trial of adjunctive buspirone 30 mg/day in patients taking an atypical antipsychotic maintenance drug, Sumiyoshi *et al.* (2007) observed no improvement in

Brief Psychiatric Rating Scale scores, although they noted improved recall on one secondary outcome measure, the Verbal Learning subscale. Two placebo-controlled pilot trials of limited size by an Iranian group found that adjunctive treatment with buspirone improved negative symptoms in patients with chronic schizophrenia taking antipsychotic maintenance drugs (Ghaleiha *et al.* 2010; Sheikhmoonesi *et al.* 2015). Wang *et al.* (2019) conducted an RCT examining buspirone's effects on cognitive function in patients with schizophrenia treated with atypical antipsychotic drugs. Repeated-measures analysis of variance showed significant differences between the group receiving buspirone cotreatment and the group receiving atypical antipsychotics alone in their arithmetic, similarities, picture completion, block design, Social Disability Screening Schedule, and Family Burden Interview Schedule scores ($P < 0.05$), but no difference was found with regard to the information, digit span test, or digit symbols scores ($P > 0.05$). The authors concluded that cotreatment with buspirone and atypical antipsychotic drugs outperformed atypical antipsychotic drugs alone in improving cognitive deficit and reducing family burden of schizophrenia (Wang *et al.* 2019). A meta-analysis conducted by two investigators systematically and independently searched English and Chinese databases for adjunctive use of buspirone and tandospirone in schizophrenia treatment. There was no efficacy for psychotic symptoms, but they did find that adjunctive buspirone may be associated with improvement in cognitive deficits in schizophrenia and extrapyramidal symptoms (Zheng *et al.* 2018). Higher-quality RCTs are needed to confirm these findings.

Adjunctive Use in Autism Spectrum Disorder

Buspirone treatment has been assessed in patients with autism spectrum disorder (ASD). In an 8-week placebo-controlled trial of adjunctive buspirone during risperidone maintenance treatment of 40 children and adolescents with ASD, Ghanizadeh and Ayoobzadehshirazi (2015) observed a 30% decline in Irritability subscale scores on the Aberrant Behavior Checklist-Community rating scale in 13 of the 16 patients taking buspirone versus 7 of the 18 patients in the placebo group, a significant treatment effect. In a three-arm, 24-week placebo-controlled trial (n = 166), Chugani *et al.* (2016) assessed the safety and efficacy of low-dosage buspirone for children with ASD. The buspirone 2.5 mg bid group showed significant improvement in irritability ratings, whereas the 5.0 mg bid group did not differ from the placebo group. In a randomized double-blind study, buspirone was as effective as methylphenidate in treating aggressive behavior in ADHD (Davari-Ashtiani *et al.* 2010). A retrospective chart review of buspirone treatment for anxiety in ASD also supported efficacy (Ceranoglu *et al.* 2019). However, Matsui *et al.* (2016) performed a meta-analysis of RCTs and single-arm trials published before October 27, 2015, with the conclusion that it remains unclear whether buspirone use has benefit for patients with ADHD.

Other Disorders

Buspirone's utility has been explored in a variety of other disorders. In a placebo-controlled study, Lee *et al.* (2005) found beneficial effects from buspirone in patients with migraine and anxiety symptoms. Buspirone was evaluated under double-blind conditions in Alzheimer's disease patients with aggressive behavior and agitation (Cantillon *et al.* 1996) and was found to be superior to haloperidol. In a retrospective study of patients from a geropsychiatric outreach program who had behavioral disturbance due to dementia, buspirone was effective at a mean dosage of 25.7 mg +-12.50 (Santa Cruz *et al.* 2017). Four RCTs have addressed buspirone use in female sexual interest/arousal disorder, finding efficacy as a function of etiology (Tuiten *et al.* 2018a, 2018b). Three case studies reported response to buspirone for sleep bruxism in children. One case involved primary sleep bruxism in a 7-year-old boy (Saglam *et al.* 2019), and the other two involved sleep bruxism associated with fluoxetine therapy (Akbas and Bilgic 2018; Colak Sivri and Akca 2016). Lastly, studies in animal models and clinical trials indicated that buspirone may be useful in treating tardive dyskinesia (Howland 2011) and L-dopa-induced and graft-induced dyskinesias of Parkinson's disease (Loane and Politis 2012).

Dosage and Administration

Buspirone is available as immediate-release tablets in strengths of 5 mg, 7.5 mg, 10 mg, 15 mg, and 30 mg. The recommended buspirone dosage for treatment of GAD is 15-20 mg/day initially, prescribed in divided doses, with increases to 30 mg/day if indicated and a maximum dosage of 60 mg/day. It should be mentioned that in the double-blind, placebo-controlled MDD trials described earlier (see the section "Mixed Anxiety-Depression"), the maximum dosage was 90 mg/day (Rickels *et al.* 1991; Robinson *et al.* 1989a, 1990). Therefore, higher buspirone dosages than those prescribed for anxiety disorders may be needed in the treatment of MDD, either as monotherapy or as augmentation of an SSRI.

Therapeutic response to buspirone differs in anxious patients naive to benzodiazepine treatment compared with patients recently treated with a benzodiazepine (DeMartinis *et al.* 2000; Schweizer and Rickels 1986). Findings of placebo-controlled efficacy trials showed that patients with GAD with either no prior benzodiazepine treatment or temporally remote benzodiazepine treatment (> 6 months previously) experienced greater improvement with buspirone therapy than did patients who either were currently receiving or had recently completed treatment with a benzodiazepine. This lower therapeutic response may reflect a subclinical benzodiazepine withdrawal syndrome (possibly exacerbated by buspirone's 1-PP metabolite). Directly switching from SSRI treatment to buspirone is not problematic.

Side Effects and Toxicology

Summarizing data from 17 clinical trials, Newton *et al.* (1986) noted the incidence of frequently reported adverse effects experienced during buspirone treatment: dizziness

(12%), drowsiness (10%), nausea (8%), headache (6%), nervousness (5%), fatigue (4%), insomnia (3%), light-headedness (3%), dry mouth (3%), and excitement (2%). A literature review of movement disorder symptoms associated with buspirone in 2020 revealed 14 cases of dyskinesia, 10 cases of akathisia, 8 cases of myoclonus, 6 cases of Parkinsonism, and 6 cases of dystonia. Cases not clearly defined were 7 cases of tension, 14 cases of incoordination, and several cases of dyskinesia, tics, and Parkinsonism (Rissardo and Caprara 2020). A case of stiff person syndrome correlated with initiation of buspirone was also reported (Sablaban and Prabhakar 2017). A case report of serotonin syndrome (Nunes and Botas 2020) included buspirone in the regimen of prescribed serotonergic medications. Buspirone lacks abuse potential, unlike alcohol and the benzodiazepines (Balster 1991). Psychomotor function studies, including evaluation of complex motor driving skills and memory tasks, have documented buspirone's lack of impairment potential in these domains (Boulenger *et al.* 1989; Greenblatt *et al.* 1994; Lucki *et al.* 1987; Smiley and Moskowitz 1986). Buspirone does not inhibit cytochrome P450 enzymes, although it does cause modest elevations of haloperidol and cyclosporin A levels. Buspirone has few significant pharmacodynamic interactions with other psychotropic drugs, apart from a potential risk of serotonin syndrome in combination with monoamine oxidase inhibitors. Since buspirone was introduced into clinical medicine, no deaths attributable solely to buspirone overdose have been reported. Buspirone remains an unusually safe and well-tolerated anxiolytic with no abuse potential.

Conclusion

Discovery of the 5-HT$_{1A}$ receptor was instrumental in linking modulation of 5-HT neurotransmission with anxiety disorders. Buspirone, a selective partial agonist of the 5-HT$_{1A}$ receptor, is the only drug in this class of antianxiety agents approved for the treatment of GAD and anxiety with associated depressive symptoms.

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[++] Dr. Robinson passed away in September 2022.

CHAPTER 24

Brexanolone and Other Neurosteroids

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History and Discovery

Reproductive steroids play a powerful role in the regulation of most systems that have been implicated in the etiology and pathogenesis of depression and specifically postpartum depression (PPD). They interact with the receptors and enzymes (metabolic and synthetic) of almost all neurotransmitters, including serotonin, dopamine, norepinephrine, glutamate, and g-aminobutyric acid (GABA) (Rubinow *et al.* 1998; Schiller *et al.* 2020). There has been great interest in understanding the role of GABA and, in particular, the disturbance of GABAergic inhibition, which plays a vital regulatory role in neuronal activity and circuits (Lee and Maguire 2014). Importantly, allopregnanolone, a neurosteroid that is the metabolite of the reproductive hormone progesterone, is a potent activator of GABA receptors, regulating their subunit composition and contributing to tonic inhibition.

Evidence demonstrating the role of allopregnanolone as an activator of GABA receptors comes from animal model work demonstrating that genetically induced interference (deficient in the GABA$_A$ receptor [GABA$_A$R] delta subunit or KCC2) with GABA receptor signaling created a mouse model of PPD (Maguire and Mody 2008), which was subsequently reversed by administration of allopregnanolone (Melon *et al.* 2018a, 2018b). In addition, animals with genetically induced GABA deficits showed abnormal activation of neural networks (prefrontal cortex and amygdala), which was repaired after administration of allopregnanolone (Melon *et al.* 2018a).

It is important to note that neuroactive steroids, such as allopregnanolone, represent a class of GABA$_A$R positive allosteric modulators (PAMs) that are pharmacologically distinct from benzodiazepines (Meltzer-Brody and Kanes 2020). Benzodiazepines act at

the synaptic level only (Sigel and Buhr 1997; Sigel and Ernst 2018), in contrast to neuroactive steroids such as allopregnanolone, which act at both synaptic and extrasynaptic GABA$_A$Rs (Abramian *et al.* 2014; Laverty *et al.* 2017; Sigel and Ernst 2018).

Clinical Trials of Brexanolone

Open-Label Study

Preclinical animal studies served as the rationale for the initial open-label trial of a proprietary formulation of allopregnanolone, brexanolone, for women with PPD. The preclinical data indicated that the rapid changes in levels of allopregnanolone in the transition from pregnancy to the postpartum period could trigger PPD in some women. Therefore, brexanolone (USAN; formerly SAGE-547 Injection), a proprietary, intravenous form of allopregnanolone, was studied as a potential treatment for severe PPD in an open-label study in 2015 (Kanes *et al.* 2017a). The initial four women who participated in the open-label study at one study site demonstrated a robust treatment response. All of the women enrolled had severe PPD (onset of symptoms in the early postpartum period), defined as a 17-item version of the Hamilton Rating Scale for Depression (Ham-D-17) score of [?] 20. The brexanolone was titrated over 12 hours to reach third-trimester allopregnanolone levels. After a 36-hour maintenance infusion, tapering occurred over 12 hours (Kanes *et al.* 2017a). The drug was well tolerated, and given that all four women showed a reduction in Ham-D scores consistent with remission of symptoms, the open-label trial was concluded and a multisite double-blind trial was begun (Kanes *et al.* 2017a).

Phase II Double-Blind Study

The Phase II double-blind, randomized, placebo-controlled trial (ClinicalTrials.gov number NCT02614547) maintained the same protocol as the initial open-label trial and was conducted from 2015 to 2016 (Kanes *et al.* 2017b). In the Phase II study, 21 women with severe PPD (Ham-D score [?] 26) who were [?] 6 months postpartum were recruited. Patients in the trial were recruited from four hospitals in the United States and randomly assigned (1:1) by computer to receive either brexanolone or placebo. The study drug (either brexanolone or placebo) was administrated as a continuous intravenous infusion over 60 hours. Both the investigators and the patients were blinded to treatment arm. The primary endpoint was Ham-D change from baseline at the 60-hour mark. All patients in the trials were followed for 1 month until day 30 (Kanes *et al.* 2017b).

Of the 21 women recruited into the study, 10 women were randomly assigned to receive brexanolone and 11 women received placebo. At the 60-hour primary endpoint assessment, the Ham-D mean reduction from baseline was 21.0 (standard error [SE] 2.9) in those receiving brexanolone, compared with an 8.8 point (SE 2.8) reduction in those receiving placebo (difference [?] 12.2, 95% CI, [?] 20.77 to [?] 3.67; $P = 0.0075$; effect size 1.2). There were no study discontinuations due to serious adverse events and no deaths. The most commonly reported side effects in the brexanolone group were dizziness and sleepiness (Kanes *et al.* 2017b).

Overall, the findings from the Phase II trial were encouraging and supported further development of brexanolone as a potential new treatment for PPD. The findings in the Phase II study led to initiation of the Phase III studies of brexanolone.

Phase III Double-Blind Studies

The Phase III trials consisted of two double-blind, randomized, placebo-controlled trials conducted at more than 30 clinical sites in the United States (ClinicalTrials.gov numbers NCT02942004 [study 1] and NCT02942017 [study 2]). Inclusion criteria were as follows: women who were 18-45 years old and within 6 months postpartum at the initial screening visit. Those enrolled demonstrated severe PPD (Ham-D score [?] 26) for one of the Phase III trials and a Ham-D score of 20-25 for the second study. Women with histories of psychosis, bipolar disorder, schizophrenia, schizoaffective disorder, or renal failure were excluded. Women enrolled in the study were randomly assigned (1:1:1) to receive either a 60-hour intravenous infusion of brexanolone 90 mg/kg/hour (BRX90), brexanolone 60 mg/kg/hour (BRX60), or placebo. Both the investigators and the patients were blinded to study treatment arm (Meltzer-Brody *et al.* 2018).

The study was conducted from August 2016 through October 2017 for both Phase III studies. Of the 375 women screened for study participation, 138 were randomly assigned in the first study to receive either BRX90 (n = 45), BRX60 (n = 47), or placebo (n = 46), and 108 women were randomly assigned in the second study to receive BRX90 (n = 54) or placebo (n = 54).

In the first study, at the 60-hour primary endpoint, the least-squares mean reduction in Ham-D score compared with baseline was 19.5 points (SE 1.2) in the BRX60 group, 17.7 points (SE 1.2) in the BRX90 group, and 14.0 points (SE 1.1) in the placebo group ([?] 5.5 [95% CI, [?] 8.8 to [?] 2.2], P = 0.0013 in the BRX60 group and 3.7 [95% CI, [?] 6.9 to [?] 0.5], P = 0.0252 in the BRX90 group). In the second study at the 60-hour primary endpoint, the least-squares mean reduction in Ham-D score compared to baseline was 14.6 points (SE 0.8) in the BRX90 group and 12.1 points (SE 0.8) in the placebo group ([?] 2.5 [95% CI, [?] 4.5 to [?] 0.5], P = 0.0160). The most common adverse events in the brexanolone groups were headache, dizziness, and sleepiness (Meltzer-Brody *et al.* 2018).

The findings of the Phase III studies demonstrated a clinically meaningful reduction in Ham-D scores that was statistically significant (Meltzer-Brody *et al.* 2018). The rapid onset of action and sustained treatment response over the 30-day study period suggested that brexanolone is a novel pharmacological treatment for PPD that could improve treatment options for women with this often severe disorder.

In sum, the development of a proprietary, intravenous form of allopregnanolone (brexanolone) as a first-in-class pharmacotherapy led to the 2019 approval by the FDA for the treatment of women with PPD. There was a 5-year period of time between the first open-label infusion of brexanolone (2015) and FDA approval of brexanolone in March 2019. The accelerated development timeline of the first approved drug for PPD and the first in its class was an exciting step forward for the field.

Structure-Activity Relations

Brexanolone is an aqueous mixture of synthetic allopregnanolone ($C_{21}H_{34}O_2$, 3a,5a-THP with a relative molecular mass of 318.5 Da) and the solubilizing agent sulfobutyl ether b-cyclodextrin (Figure 24-1). This compound is structurally identical to allopregnanolone, a breakdown product of progesterone.

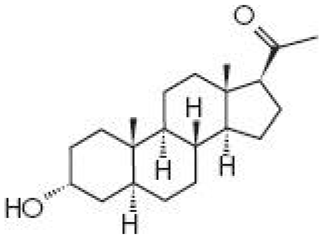

FIGURE 24-1. Chemical structure of brexanolone.

Dosage Forms and Administration

Brexanolone is available at an allopregnanolone concentration of 100 mg/20 mL. Zulresso (brexanolone) injection for intravenous use is available in single-use vials at a concentration of 100 mg/20 mL (5 mg/mL).

Brexanolone requires further dilution prior to administration. Detailed instructions are provided in the product labeling (Sage Therapeutics 2019).

Pharmacological Profile

Brexanolone is a PAM of the $GABA_AR$, with allopregnanolone being the endogenous neuroactive steroid.

Brexanolone is more than 99% protein bound. It is administered intravenously over 60 hours with a titration schedule.

Pharmacokinetics

Brexanolone is available only via the intravenous route because of the poor bioavailability of allopregnanolone. However, depression trials have been conducted with zuranolone (formerly SAGE-217), an oral synthetic neurosteroid and PAM of $GABA_A$ receptors. Zuranolone has been tested in populations with major depressive disorder (MDD) and PPD with success (Deligiannidis *et al.* 2021; Gunduz-Bruce *et al.* 2019), and in August 2023, it became the first oral medication to receive FDA approval for the treatment of PPD in adults (U.S. Food and Drug Administration 2023).

When brexanolone is given intravenously, it exhibits dose-proportional pharmacokinetics over a dosage range of 30-270 mg/kg/hour. Brexanolone is metabolized by non-cytochrome P450 pathways into three inactive metabolites through keto-reduction, glucuronidation, and sulfation, with a terminal half-life of 9 hours. These metabolites are eliminated in feces (47%) and urine (42%), with less than 1% eliminated in the urine as unchanged drug. The total plasma clearance of brexanolone is approximately 1 L/hour/kg. Brexanolone should be avoided in end-stage renal disease with an estimated glomerular filtration rate of less than 15 mL/minute/1.73 m^2 because of the potential accumulation of the solubilizing agent betadex sulfobutyl ether sodium (Sage Therapeutics 2019).

Mechanism of Action

Brexanolone is a neuroactive steroid that acts as an antidepressant for women with PPD. Although the etiology of PPD is not fully understood, allopregnanolone concentrations dramatically decline after childbirth, and GABA system dysfunction is thought to play a critical role in PPD. Brexanolone is a PAM of the $GABA_A$Rs. Of note, PAMs of $GABA_A$Rs, such as allopregnanolone, are pharmacologically distinct from benzodiazepines. These neurosteroids bind both synaptic and extrasynaptic receptors, with allopregnanolone being one of the most potent modulators (Meltzer-Brody and Kane 2020). A recent study found that brexanolone infusion reduced levels of the inflammatory markers tumor necrosis factor-a and interleukin-6 and inhibited their response to the inflammatory immune activators lipopolysaccharide and imiquimod, and these effects were correlated with Ham-D score improvement (Balan *et al.* 2023). Thus, brexanolone may achieve its remarkable and sustained therapeutic effects by inhibiting these pathways and/or by changing the sensitivity of immune cells to subsequent stimulation by inflammatory activators.

Indications and Efficacy

In 2019, brexanolone was approved by the FDA for treating PPD in adults. Brexanolone went through one Phase II and two Phase III trials that were multicenter, prospective, double-blind, and placebo controlled for a total of 267 subjects ages 18-45 years (Kanes *et al.* 2017b; Meltzer-Brody *et al.* 2018). The primary efficacy endpoint in all studies was a change in Ham-D score from baseline to the infusion end (hour 60), with a secondary endpoint being Ham-D score at day 30. Brexanolone produced a statistically significant improvement in depressive symptoms when compared with placebo. One criticism of these studies of brexanolone was their limited follow-up, to 30 days after infusion. A subsequent clinical study of patients treated after FDA approval of the drug followed 11 patients to 90 days after treatment and showed continued efficacy, with Ham-D scores lower than at hour 60 (Patterson *et al.* 2022).

Investigative Applications for Neurosteroids

Brexanolone for the treatment of PPD has been studied in adolescents ages 15-17 years, with findings similar to those in the adult trials. Brexanolone was generally well tolerated in this population with Ham-D response being achieved by 75% of participants at the end of infusion (hour 60) and by 89.5% of participants at the end of the trial (day 30) (Riesenberg *et al.* 2022). SAGE-547 (brexanolone) has also been studied in populations with super-refractory status epilepticus and essential tremor (Ellenbogen *et al.* 2016; Rosenthal *et al.* 2017). Allopregnanolone and related neuroactive steroids such as pregnenolone and ganaxolone have been investigated in a number of other psychiatric and medical conditions including major neurocognitive disorders, substance use disorders, stress disorders, and seizure disorders (Besheer *et al.* 2010; Lattanzi *et al.* 2021; Morrow *et al.* 2020; Rasmusson *et al.* 2017; Tomaselli and Vallee 2019).

Zuranolone (SAGE-217; Sage Therapeutics) is a neuroactive steroid being investigated as an oral treatment for MDD, PPD, insomnia, bipolar depression, and Parkinson's disease (Althaus *et al.* 2020; Bullock *et al.* 2021, 2022; Deligiannidis *et al.* 2021; Gunduz-Bruce *et al.* 2019). It is a GABA$_A$R PAM that has a pharmacokinetic profile and mechanism of action that are suitable for oral once-daily dosing (Deligiannidis *et al.* 2021; Hoffmann *et al.* 2020). Zuranolone was granted a breakthrough therapy designation by the FDA in October 2021 (Biogen 2021a). Zuranolone's new drug application has been accepted by the FDA, and a priority decision review was conducted in August 2023 (Biogen 2023). On August 4, 2023, zuranolone became the first oral medication to receive FDA approval for the treatment of PPD in adults (U.S. Food and Drug Administration 2023).

Major Depressive Disorder Trials

In a double-blind Phase II trial of zuranolone in patients with moderate to severe major depressive disorder, 89 patients were enrolled to receive either 30 mg of SAGE-217 or placebo once daily for 14 days. The primary endpoint was a change in Ham-D score from baseline to day 15. Forty-five patients were randomly assigned to the SAGE-217 group and 44 to the placebo group. The least-squares mean reduction in Ham-D score at day 15 for the SAGE-217 group was 17.4 points (SE 1.3), and the reduction for the placebo group was 10.3 points (SE 1.3; 95% CI, [?] 10.2 to [?] 3.9; *P* < 0.001) (Gunduz-Bruce *et al.* 2019). A number of Phase III trials with zuranolone are under way for treatment of MDD, with results pending, including successful trials when zuranolone is co-initiated with other antidepressant therapy (Biogen 2021b). However, recent data reported from the Phase III MOUNTAIN trial of zuranolone treatment in adults with MDD indicated that the trial did not meet its primary endpoints (Clayton *et al.* 2023).

Postpartum Depression Trials

A Phase III double-blind, randomized, placebo-controlled trial of zuranolone was conducted among patients with severe PPD (Ham-D score [?] 26) from 2017 to 2018. As in the brexanolone trials, patients were women ages 18-45 years with a major depressive episode occurring in the third trimester or within the first 4 weeks postpartum who were [?] 6 months postpartum at the time of enrollment. The trial enrolled 153 subjects, 77 of whom were randomly assigned to receive 30 mg of zuranolone daily for 14 days and 76 of whom were in the placebo group. The primary endpoint was a change in Ham-D score from baseline to day 15. The primary endpoint was achieved, with the zuranolone group reporting significantly lower Ham-D scores at day 15 compared with the placebo group (least-squares mean, [?] 17.8 points vs. [?] 13.6 points; 95% CI [?] 6.9 to [?] 1.5; *P* = 0.003) (Deligiannidis *et al.* 2021). Subjects receiving zuranolone had a sustained greater reduction in Ham-D scores in comparison with the placebo group beginning at day 3 and continuing through the last follow-up at day 45. Phase III trials with zuranolone are ongoing, and the current data reflect an exciting new oral treatment for postpartum depression.

Other Trials

Zuranolone has also been investigated for the treatment of insomnia, Parkinson's disease, and bipolar depression. Data from clinical trials are not yet available for bipolar depression, but promising results have been reported from the insomnia and Parkinson's trials. A Phase I double-blind, placebo-controlled trial (ClinicalTrials.gov number NCT03284931) for the use of zuranolone to treat insomnia enrolled 45 patients who were given varying doses of zuranolone (30 mg vs. 45 mg) or placebo during a single sleep cycle. Patients who received zuranolone reported significantly greater improvements in sleep efficiency when compared with the placebo group (30 mg, 84.6%; 45 mg, 87.6%; placebo, 72.9%; $P < 0.001$ for both dosages) (Bullock *et al.* 2022). Results from a Phase II open-label trial of zuranolone for Parkinson's disease have reported promising data for the use of zuranolone in reducing parkinsonian tremor (Bullock *et al.* 2021).

Side Effects and Toxicology

Brexanolone

Brexanolone has a black box warning regarding excessive sedation and sudden loss of consciousness. During clinical studies, 5% of brexanolone-treated subjects experienced excessive sedation that necessitated dosage interruption or reductions, and 4% experienced loss of consciousness. To address these rare but serious side effects, the FDA mandated several safety parameters, including a Risk Evaluation and Mitigation Strategy (REMS), which requires continuous pulse oximetry and every-2-hour sedation scale monitoring; in addition, patients must be accompanied by an adult during interactions with their infant for the duration of the infusion (U.S. Food and Drug Administration Center for Drug Evaluation and Research 2016). The Zulresso REMS program requires that all health care settings, pharmacies, physicians, and patients enroll in the restricted program. If a patient becomes sedated, the infusion should be stopped until the patient returns to the baseline alertness level. At that time, the infusion could be resumed at a lower, better-tolerated dose. If the patient becomes hypoxic at any time during the infusion, it should be stopped and not restarted.

Information about the REMS program for brexanolone is available from the FDA website (www.fda.gov), which hosts a database of all REMS programs and their unique requirements. A Patient Medication Guide is also provided as part of the brexanolone product labeling (Sage Therapeutics 2019).

Additional common adverse reactions with brexanolone (incidence [?] 5% and at least twice the rate of placebo) include mild sedation or somnolence (21%), presyncope, dizziness, or vertigo (13%), dry mouth (11%), and flushing or hot flashes (5%) (Sage Therapeutics 2019).

Pregnancy

No human data on use of brexanolone in pregnancy are available. Previous studies in animal models at twice the maximum recommended human dosage suggested fetal harm. Subjects in the brexanolone clinical trial had negative pregnancy tests and used approved birth control for 30 days after infusion.

Lactation

According to data from 12 women infused in the clinical trials, brexanolone is transferred to and present in breast milk (Hoffmann *et al.* 2019). The maximum relative infant dosage during infusion was 1%-2% of the maternal weight-adjusted dosage, and concentrations of brexanolone were < 10 ng/mL 36 hours after the end of infusion. Additionally, brexanolone has low oral bioavailability in adults (< 5%), so infant exposure is thought to be low as well.

Zuranolone and Other Neurosteroids

Reported side effects of zuranolone and related neurosteroids are similar to those of the brexanolone injection, but no reports of loss of consciousness have occurred to date. Common reported adverse events across zuranolone clinical trials include headache, dizziness, nausea, somnolence, dry mouth, and sedation (Bullock *et al.* 2021, 2022; Deligiannidis *et al.* 2021; Gunduz-Bruce *et al.* 2019).

Drug-Drug Interactions

There may be an increased risk for excessive sedation and loss of consciousness when brexanolone is used with other CNS depressants. Clinicians should be particularly careful with coadministration of GABAergic medications, including opioids and benzodiazepines, because these agents could potentiate the sedative effects. Caution should be taken with patients who have an active alcohol use disorder. Additionally, in placebo-controlled studies, patients with concomitant brexanolone and antidepressant use reported more sedation than did patients receiving placebo (Kanes *et al.* 2017b; Meltzer-Brody *et al.* 2018; Sage Therapeutics 2019).

Conclusion

Brexanolone and zuranolone are currently the only FDA-approved treatments for PPD. Brexanolone is the synthetic form of allopregnanolone, a breakdown product of progesterone, levels of which plummet at the time of delivery. Zuranolone has a pharmacokinetic profile and mechanism of action that are suitable for oral once-daily dosing. These neuroactive steroids are PAMs of the GABA system, and dysfunction in this system's signaling has been implicated in PPD. PPD is the most common complication of childbirth, with estimates of around 15%. Unfortunately, it has been very difficult to treat to remission, and many women suffer for prolonged periods of time, with negative consequences that extend to their families. Brexanolone and zuranolone are rapid-acting, with novel mechanisms of action and delivery systems, which makes them different from typical antidepressant treatments. Long-term benefits remain largely unknown, although one study has shown continued efficacy for brexanolone at 90 days after infusion (Patterson *et al.* 2022).

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Antipsychotics

CHAPTER 25

Classic Antipsychotic Medications

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History and Discovery

Before the introduction of classic antipsychotic medications in the 1950s, treatment for psychotic disorders consisted primarily of institutional confinement and supportive care, with minimal control of psychotic symptoms. The discovery of chlorpromazine, the first of the "classic" antipsychotics, was serendipitous and owes much to the observations of a French surgeon, Henri Laborit, who noted that chlorpromazine, when used as an adjunct to anesthesia, calmed patients significantly after surgery. Laborit recommended its use to two French psychiatrists, Jean Delay and Pierre Deniker, who used it successfully for psychotic patients. Heinz Lehmann was the first to use chlorpromazine in North America (in Montreal, Canada). In the early 1960s, the first large-scale placebo-controlled trials were conducted within the U.S. Veterans Administration system.

After the successes of chlorpromazine, numerous other phenothiazines were synthesized by modification of the side chains on the phenothiazine rings. Subsequently, several nonphenothiazine antipsychotics, such as haloperidol, were introduced. The last of these drugs approved by the FDA was molindone, introduced in 1975. Of 51 classic antipsychotic drugs (representing eight different chemical classes) available in the world, 9 are currently available in the United States.

The ability of chlorpromazine and other conventional antipsychotics to suppress psychotic symptoms (delusions, hallucinations, and disorganization) had a profound impact on chronically hospitalized psychiatric populations worldwide. Many psychiatric patients were discharged from state hospitals to the community. This period of deinstitutionalization led to a decrease in the number of patients in state and county mental hospitals in the United States from 559,000 in 1955 to 338,000 in 1970 to 107,000 in 1988, an 80% decrease over 30 years. Initially, this decrease led to enthusiasm about the possibility that individuals with schizophrenia and other psychoses would be able to function well in the community. However, it soon became apparent that improvement with antipsychotic treatment was incomplete. In addition, poor treatment adherence--with subsequent relapses--led to frequent rehospitalization (i.e., the "revolving door" phenomenon).

As psychiatrists began using chlorpromazine, they observed that treated patients often manifested signs and symptoms of parkinsonism. Along with other side effects such as dystonia and akathisia, these symptoms are collectively called extrapyramidal side effects (EPS). Because of the high prevalence of these movement disorders among patients receiving antipsychotic treatment, many psychiatrists believed EPS to be an unavoidable accompaniment of antipsychotic action; in fact, the onset of some EPS was considered to indicate the minimal effective antipsychotic dosage (i.e., the "neuroleptic threshold"). The first report of persistent orobuccal movements (later called tardive dyskinesia) came from France in 1959. The pervasiveness of debilitating short-term and long-term motor side effects associated with classic antipsychotic drugs led to a search for agents that would be at least as efficacious but without the risk of EPS.

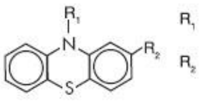
Clozapine, a dibenzodiazepine synthesized in 1959, was the first antipsychotic drug without EPS (i.e., an atypical antipsychotic). It was initially marketed in Europe in 1972 but was withdrawn in some countries in 1975 after several reports of fatalities secondary to agranulocytosis. Clozapine was not introduced in the United States until 1989, after convincing studies demonstrated its efficacy in antipsychotic-refractory schizophrenia. Other atypical agents (also called second-generation antipsychotics [SGAs]) have been launched in the past three decades and are reported to be associated with lower levels of EPS and a broader spectrum of efficacy; of the more than 20 SGAs currently being marketed, 13 are available in the United States (see Chapters 26-35 in this textbook). Since the introduction of these newer agents, use of the classic antipsychotics (also called traditional, conventional, or first-generation antipsychotics [FGAs]) has declined, especially in the United States; FGAs account for approximately 5% of all antipsychotic prescriptions in the country. Results of several government-sponsored effectiveness studies--for example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)--have challenged the prevailing worldview of the greater effectiveness of SGAs over FGAs and have reinvigorated interest in the utility and clinical applicability of classic antipsychotics.

Structure-Activity Relations

Phenothiazines

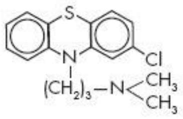
Members of the phenothiazine class of classic antipsychotics share the same basic phenothiazine ring but differ in substitutions at both their R1 and R2 positions (Figure 25-1). Based on the side chain attached to the nitrogen atom in the middle ring (R1), the phenothiazines are further subdivided into three subtypes: aliphatic, piperidine, and piperazine phenothiazines.

Basic phenothiazine ring

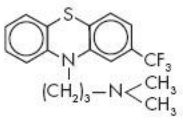


A. Phenothiazines

1. Aliphatic

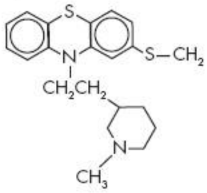


Chlorpromazine

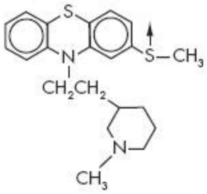


Triflupromazine

2. Piperidine

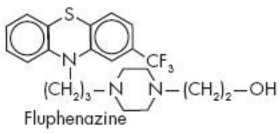


Thioridazine

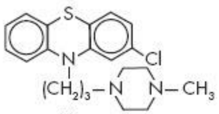


Mesoridazine*

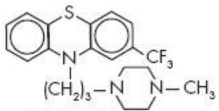
3. Piperazine



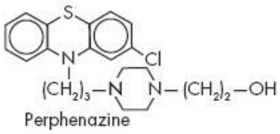
Fluphenazine



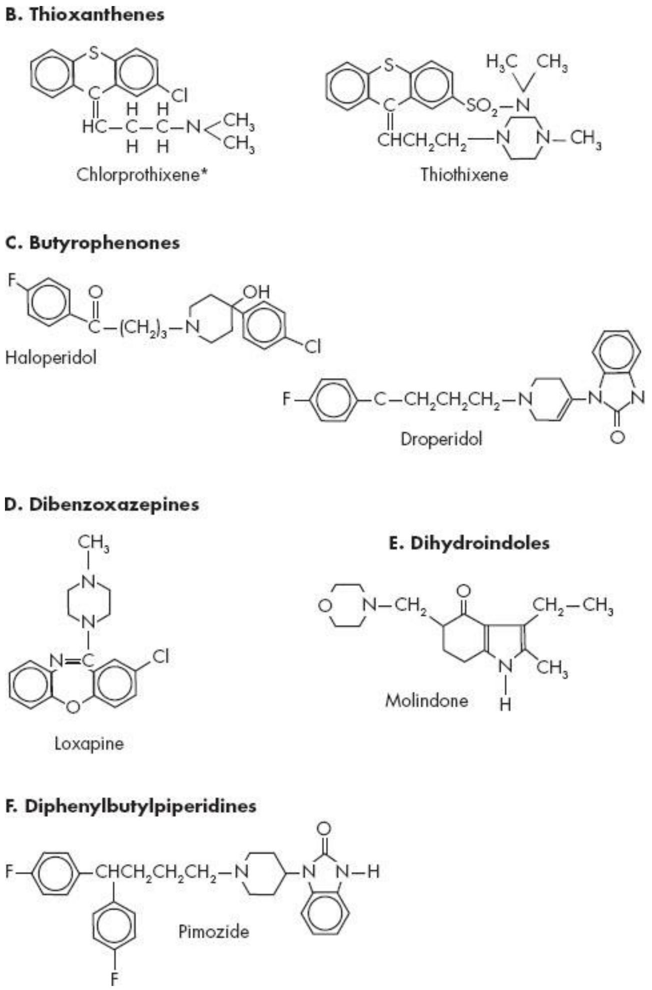
Prochlorperazine



Trifluoperazine



Perphenazine


B. Thioxanthenes

C. Butyrophenones

D. Dibenzoxazepines

E. Dihydroindoles

F. Diphenylbutylpiperidines

FIGURE 25-1. Chemical structures of various classic antipsychotics.

*No longer available in the United States.

Aliphatic Phenothiazines

The aliphatic phenothiazines share a dimethylamide substitution at their tenth carbon. Chlorpromazine (Thorazine or Largactil) is the prototypical member of this class and remains the aliphatic phenothiazine most widely used throughout the world. With a chlorine atom attached to its second carbon, chlorpromazine is heavily sedating because of its high level of anticholinergic, anti-a-adrenergic, and antihistaminergic actions.

Piperidine Phenothiazines

Piperidine phenothiazines--for example, thioridazine (Mellaril) and its metabolite, mesoridazine (Serentil)--are named for the presence of a piperidine ring at their tenth carbon. Although members of this group have similar efficacy and side effects compared with aliphatic phenothiazines, they are notable for having a less potent effect on nigrostriatal dopamine$_2$ (D_2) receptors and a higher level of anticholinergic activity; consequently, they are associated with a lower frequency of EPS. The use of these agents has been virtually extinguished by a black box warning about significant QTc prolongation that was added to their product label in 2000.

Piperazine Phenothiazines

With a substitution of a piperazine group at the tenth carbon of a phenothiazine, the piperazines have much greater D_2 receptor blockade and a lower affinity for muscarinic, a-adrenergic, and histaminergic receptors. Some of the most potent conventional antipsychotics available in the United States, including fluphenazine (Prolixin), perphenazine (Trilafon), and trifluoperazine (Stelazine), belong to this class. The well-known antiemetic prochlorperazine (Compazine) is also part of this class; although approved for the treatment of psychosis, it is rarely used as an antipsychotic.

Thioxanthenes

Structurally and pharmacologically similar to the phenothiazines, the thioxanthenes also differ widely in their pharmacological profiles based on similar side chain substitutions (see Figure 25-1). For instance, chlorprothixene shares the same dimethylamide and chloride substitution as chlorpromazine, with which it also shares its pharmacological profile. Thiothixene (Navane) has both a piperazine side chain and a strongly electrophilic substitution $[SO_2N(CH_3)CH_3]$, thus sharing the pharmacological profile of the piperazines.

Butyrophenones

The butyrophenone class has a piperidine ring with a three-carbon chain ending in a carbonyl-substituted p-fluorobenzene ring. Haloperidol, arguably the best-known classic antipsychotic, is the most widely used agent in this class. Haloperidol and other members of this class are strong dopamine receptor antagonists and show little antimuscarinic, antihistaminergic, and antiadrenergic activity.

Dibenzoxazepines

Loxapine, the only FDA-approved agent in the dibenzoxazepine class, is composed of a tricyclic ring structure with a seven-member central ring. It has a piperazine side

chain and chlorine at position R2 (see Figure 25-1). It exhibits an intermediate level of D_2 blockade, as well as some serotonin$_2$ (5-HT_2) antagonism. Its side-effect profile is characterized by intermediate sedation and autonomic effects. Loxapine has the distinction of being the most "atypical" of the classic antipsychotics because it is structurally similar to the dibenzodiazepine clozapine. Another notable feature of loxapine is that one of its metabolites, amoxapine, is marketed as an antidepressant.

Dihydroindoles

Molindone is the only member of the dihydroindoles available in the United States. Sharing a similar structure with the indolamines (see Figure 25-1), such as serotonin, molindone has the distinction of being the only classic antipsychotic not associated with any weight gain or a lowering of the seizure threshold.

Diphenylbutylpiperidines

Pimozide, the only agent in the diphenylbutylpiperidine class available in the United States, is approved only for the treatment of Tourette syndrome and has the distinction of possessing the highest selectivity and potency for dopamine D_2 receptors among the conventional antipsychotics. It significantly prolongs the QTc interval, and this has limited its use. Derived from benperidol, pimozide shares many characteristics of the butyrophenones (see Figure 25-1).

Benzamides and Iminodibenzyl Agents

Sulpiride, the prototypical substituted benzamide, is a relatively selective dopamine D_2 antagonist and lacks significant activity on cholinergic, histaminergic, or noradrenergic receptors. Because of this relative selectivity and a lower propensity to cause EPS, sulpiride is one of the more common classic antipsychotics used in Europe. No classic antipsychotic agent from either the benzamide or the iminodibenzyl class is available in the United States.

Pharmacological Profile

The classic conventional antipsychotic drugs have a multitude of effects on various physiological variables through their actions on different neurotransmitter systems. The antipsychotic effects of these agents are believed to occur primarily through antagonism of D_2-type dopaminergic receptors. Therapeutic and adverse effects of D_2 antagonism have been conceptualized in the context of the major dopaminergic tracts present in the brain, which include the mesocortical, mesolimbic (A10), tuberoinfundibular (A12), and nigrostriatal (A8 and A9) tracts.

The effect of D_2 receptor blockade on the mesolimbic dopaminergic systems is believed to represent the putative mechanism of action of conventional antipsychotics, but D_2 blockade in other tracts is believed to result in a number of adverse cognitive and behavioral side effects. Such side effects are common in both animals and human subjects. D_2 receptor antagonism in the mesocortical dopaminergic pathway leads to a blunting of cognition (bradyphrenia) and avolition-apathy (sometimes called the neuroleptic-induced deficit syndrome), which can be difficult to differentiate from the primary negative symptoms of schizophrenic illness itself.

Blockade of the tuberoinfundibular tract projecting to the hypothalamus and pituitary gland results in multiple neuroendocrine side effects processed through the pituitary gland. Although dopamine is involved in increasing the release of most pituitary hormones, it is actually responsible for the tonic inhibition of prolactin release. With significant dopaminergic blockade of the tuberoinfundibular tract, prolactin release is no longer prevented, and the release of other pituitary hormones is no longer increased. High levels of prolactin combined with low levels of follicle-stimulating hormone and luteinizing hormone often result in amenorrhea, galactorrhea, gynecomastia, decreased bone density, impaired libido, and erectile dysfunction.

High levels (exceeding 78%) of D_2 dopaminergic blockade within the nigrostriatal system, which projects to the basal ganglia and caudate, produce some of the most undesirable side effects of conventional antipsychotics. Movement disorders or EPS such as akathisia, rigidity, and hypokinesia were once believed to be necessary "evidence" of a therapeutic antipsychotic dosage. However, the advent of the new-generation antipsychotics that are associated with minimal EPS conclusively refuted this misconception. At higher levels of D_2 blockade, one may also observe dystonia, catalepsy, and a rigid, immobile catatonic state.

Classic antipsychotic agents have varying degrees of activity at serotonergic, cholinergic, noradrenergic, histaminergic, and other nondopaminergic receptors. Although it is unclear whether any of these activities contribute to or interfere with their effectiveness in the treatment of psychotic symptoms, they clearly result in a variety of adverse effects. Because of differences in the pharmacological activity of different classic antipsychotic agents at these receptors, there are predictable differences in their side-effect profiles.

Pharmacokinetics

Generally, the pharmacokinetic profiles of the conventional antipsychotics remain poorly understood. Even for some of the more extensively studied agents, many hundreds of potential metabolites remain undiscovered, and the physiological activity of several metabolites has yet to be adequately defined. Nonetheless, certain general statements can be made about the classic antipsychotics as a group.

Administration and Absorption

Many conventional antipsychotics were available in both oral and intramuscular formulations. Currently there are three antipsychotics available for intramuscular use: chlorpromazine, fluphenazine, and haloperidol. Although common in the past, intravenous usage of parenteral formulations of antipsychotics is not FDA approved. Peak plasma levels with oral preparations are generally reached in 1-4 hours, with these levels being reached slightly more rapidly with liquid concentrates. Oral preparations are extensively metabolized in the liver during their first pass through portal circulation by undergoing a range of transformations, including glucuronidation, oxidation, reduction, and methylation. Steady-state levels are reached in a period of four to five times the half-life of the drug in question.

Intramuscular administration produces faster, more predictable absorption, resulting in peak plasma levels in 30-60 minutes and clinical efficacy as early as 15 minutes.

With intramuscular or intravenous administration, plasma levels may be as much as four times the levels of the oral route because of circumvention of the hepatic first-pass metabolism.

Although 10 classic antipsychotics are available in a long-acting (depot) formulation around the world, haloperidol and fluphenazine are the only classic antipsychotics currently available in such a formulation in the United States. The currently available decanoate forms of both haloperidol and fluphenazine are administered through injection into a major muscle, and the drug is slowly released to the bloodstream over time. As the esterified version of the drug diffuses into other tissues, the ester chain is hydrolyzed, resulting in the smooth release of the drug in question. Fluphenazine decanoate can be given every 2-3 weeks on the basis of its half-life of 7-10 days, whereas haloperidol decanoate may be given every 4 weeks because of its longer half-life. The bioavailability of intramuscular relative to oral administration is two times greater.

Distribution

Most conventional antipsychotics are highly protein bound (85%-90%). This feature is important when other highly protein-bound medications are used concomitantly because of the risk of increasing levels of free or unbound drugs into the toxic range. The antipsychotic drugs are highly lipophilic, which allows unbound portions of the drug to readily cross the blood-brain barrier, with concentrations two times higher in the brain than in the peripheral circulation. The drugs also readily cross the placenta to the fetus in pregnancy.

Metabolism

The conventional antipsychotics are metabolized in the liver by hydroxylation and demethylation to forms that are more soluble and readily excreted by the kidneys and in the feces. Many of these compounds undergo further glucuronidation and remain active as dopamine receptor antagonists. Because of the many active metabolites of the antipsychotic agents, it has not been possible to obtain meaningful correlations between plasma levels and clinical response. Variables such as age, genetic variability between individuals, and coadministration of other drugs cause plasma levels to vary 10-to 20-fold between individuals. The majority of conventional antipsychotics are metabolized by the cytochrome P450 (CYP) enzyme subfamilies. Because CYP2D6 is important for the metabolism of many of these antipsychotics, genetic variation in the rate of 2D6 metabolism should be considered. CYP1A2 and 3A4 subfamily enzymes are also involved in the metabolism of some classic antipsychotics, and this effect may be relevant to understanding drug-drug interactions of those agents.

Excretion

The major routes of excretion of the classic antipsychotics are through urine and feces by way of bile. These drugs are also excreted in sweat, saliva, tears, and breast milk. Elimination half-life varies from 18 to 40 hours for these drugs. Lower dosages of antipsychotics are generally needed for older adults because of decreased renal clearance. Because of the long elimination half-lives of the classic antipsychotics, once-a-day dosing is possible for each of these agents after stabilization.

Mechanism of Action

Dopamine has been at the center of neurobiological theories of psychosis for the past half-century, and even today, all agents approved as antipsychotics share the single common attribute of D_2 receptor antagonism. Amphetamine intoxication served as a drug-induced model of the positive symptoms of schizophrenia. Drugs that blocked dopaminergic receptors, specifically the D_2 receptor, were noted to have greater efficacy and potency as antipsychotics. Because dopaminergic agonists exacerbate psychosis and dopaminergic blockade treats it, dopamine has held central importance in our conceptualization of the neuropharmacology of schizophrenia.

Indications and Efficacy

Schizophrenia and Schizoaffective Disorder

Classic antipsychotics are best known for the acute and maintenance treatment of the psychotic (also known as positive) symptoms of schizophrenia and schizoaffective disorder. The major putative mechanism of action is through D_2 blockade of the mesolimbic tract. In many patients, this blockade results in a measurable decrease in the positive symptoms of schizophrenia, including hallucinations, delusions, and disorganization (Tandon *et al.* 2010, 2013). However, negative and cognitive symptoms of schizophrenia respond less robustly. In fact, they may be worsened by blockade of mesocortical tracts that play roles in cognition and hedonic reinforcement.

The failure to improve the negative symptoms of schizophrenia is one of the major drawbacks of the classic antipsychotics. In fact, the EPS induced by the FGAs can worsen negative and cognitive symptoms by inducing bradykinesia and bradyphrenia. Another major limitation is the lack of improvement of positive symptoms (i.e., refractoriness) in about 25% of patients with schizophrenia and partial response (i.e., treatment resistance) in another 25%.

Substance-Induced Psychosis

As noted previously, conventional agents can reverse the psychosis associated with acute and chronic amphetamine intoxication and that associated with cocaine use. However, the risk of acute dystonia must be considered in these populations, because dopamine receptor downregulation is common, resulting in greater sensitivity to rapid D_2 blockade. Results in treatment of psychosis secondary to drugs acting in nondopaminergic mechanisms (such as hallucinogens) are less satisfactory, although there may be some role for the classic antipsychotics in treating phencyclidine psychosis.

Personality Disorders

Although any personality disorder can be associated with transient psychotic features emerging under stressful conditions, Cluster B disorders are most often associated with this phenomenon. Treatment for transient psychotic episodes has included short-term use of low dosages of a high-potency antipsychotic. Although some symptoms

of personality disorders may be amenable to such pharmacological treatment, long-term conventional antipsychotic treatment is not recommended.

Mood Disorders

The utility of antipsychotic agents in the treatment of mood disorders with psychotic features is well known. However, their utility in the treatment of nonpsychotic depression and bipolar disorder is described as well. Several conventional antipsychotics (such as thioridazine) are FDA approved for the treatment of depression and anxiety without overt psychosis. However, they are no longer used for this purpose because of the availability of other, more effective and better-tolerated agents. The utility of conventional agents as adjuncts to mood stabilizers in the treatment of patients with bipolar and related disorders has been well described, both in the acute management of mania and in the maintenance treatment of bipolar disorder with severe mood disturbance or psychotic features. However, the newer atypical antipsychotics have largely replaced conventional antipsychotics in the management of bipolar disorder.

Tourette Syndrome

The tics present in Tourette syndrome are believed to be due to a hyperdopaminergic state that is amenable to treatment by dopamine receptor antagonists. Pimozide is the only conventional antipsychotic with this indication, which is its only FDA-approved indication.

Huntington's Disease

Although there is no cure for Huntington's disease, the psychosis and choreiform movements associated with this disease may be ameliorated by dopamine receptor antagonism. Several conventional antipsychotics carry FDA indications for treatment of this disease.

Nausea, Emesis, and Hiccups

The lower-potency antipsychotics exert a potent antiemetic effect through histamine_1 (H_1) receptor antagonism. This effect is closely related to their original role in reducing perioperative stress and emesis. Many well-known antiemetics, such as promethazine (Phenergan), are phenothiazines with a short-chain substitution. In addition, chlorpromazine is approved for oral or intramuscular therapy of intractable hiccups.

Side Effects and Toxicology

As noted earlier, side-effect profile--rather than efficacy in treating psychosis--is used to differentiate the conventional antipsychotics (Dold *et al.* 2015). These agents serve as antagonists at four major neurotransmitter receptor systems in the CNS: the dopamine type 2 receptor family (D_2, D_3, and D_4), muscarinic cholinergic receptors (M_1), a-adrenergic receptors (a_1 and a_2), and histamine receptors (H_1) (Table 25-1).

TABLE 25-1. Relative affinities of classic antipsychotics to various neurotransmitter receptors

	Chlorpromazine	Thioridazine	Perphenazine	Trifluoperazine	Fluphenazine	Thiothixene	Haloperidol	Loxapine	Mol
D_1	High	--	High	High	High	Moderate	High	High	Lov
D_2	High	Very high	Very high	Very high	Very high	Very high	Very high	Very high	Ver
D_3	High	Very high	Unknown	Unknown	Very high	Unknown	Very high	Unknown	Unk
D_4	High	Very high	Unknown	High	Very high	Unknown	Very high	Very high	Lov
H_1	High	High	Moderate	Moderate	High	Moderate	Low	High	Ver
M_1	High	High	Low	Low	Low	Low	Low	Moderate	Nor
a_1	Very high	Very high	High	High	High	Moderate	Low	High	Lov
a_2	Moderate	Very high	Moderate	Low	Low	Moderate	Low	Low	Mo
5-HT_1	Low	Low	Low	Low	Low	Low	Low	Low	Lov
5-HT_2	High	High	Moderate	Moderate	Moderate	Moderate	Moderate	Very high	Lov

Note. Receptor families: dopamine (D_1, D_2, D_3, D_4), histamine (H_1), muscarinic cholinergic (M_1), a-adrenergic (a_1, a_2), and serotonergic (5-HT_1, 5-HT_2).

The therapeutic action of the classic antipsychotics in ameliorating the positive symptoms of schizophrenia is believed to be due to D_2 blockade in the mesolimbic dopamine tract. Blockade of D_2 receptors in the mesocortical, nigrostriatal, and tuberoinfundibular systems leads to the tract-related side effects described earlier in this chapter (see section "Pharmacological Profile"). Lower-potency agents have greater antihistaminergic, anticholinergic, and antiadrenergic actions. However, they have fewer D_2-related side effects because of their lower affinity to D_2 receptors and high anticholinergic activity.

Higher-potency agents, such as haloperidol, produce more D_2-related movement disorders and prolactin elevation but otherwise have a cleaner side-effect profile, having fewer anticholinergic, antiadrenergic, and antihistaminergic side effects. Anticholinergic action often leads to dry mouth (xerostomia), blurred vision (mydriasis), constipation, urinary retention, sinus tachycardia, confusion, impaired cognition, paralytic ileus, exacerbation of open-angle glaucoma, and drowsiness. Antagonism of a_1-adrenergic receptors is associated with orthostatic hypotension, QTc prolongation, reflex tachycardia, dizziness, incontinence, and sedation. Antagonism of a_2 receptors can be associated with retrograde ejaculation and priapism. Antagonism of H_1 receptors leads to sedation, drowsiness, and weight gain.

The frequencies of adverse reactions to classic antipsychotic agents are summarized in Table 25-2.

TABLE 25-2. Incidence of adverse reactions to classic antipsychotics at therapeutic dos

	Phenothiazines						Butyrophenone
	Chlorpromazine	**Mesoridazine***	**Thioridazine**	**Fluphenazine**	**Perphenazine**	**Trifluoperazine**	**Haloperidol**
Cognitive effects							
Drowsiness, sedation	High	High	High	Low	Moderate	Low	Low
Insomnia, agitation	Low	Low	Low	Low	Low	Low	Moderate
Extrapyramidal effects							
Parkinsonism	Low to moderate	Low to moderate	Low	High	Moderate	Moderate to high	High
Akathisia	Low	Moderate	Low	High	Moderate	High	High
Dystonic reactions	Low	Low	Low	High	Moderate	Moderate	High
Cardiovascular effects							
Orthostatic hypotension	High	High	High	Low	Low	Low to moderate	Low
Tachycardia	Moderate	Moderate	High	Low	Low	Low	Low
ECG abnormalities	Moderate	Low	Moderate	Low	Low	Low	Low
Cardiac arrhythmias	Low	Moderate	Moderate	Low	Low	Low	Moderate
Anticholinergic effects							
	High	High	High	Low	Low	Low	Low
Endocrine effects							
Sexual dysfunction	Moderate	Moderate	High	Moderate	Moderate	Moderate	Moderate
Galactorrhea	Moderate	Moderate	Moderate	High	Moderate	Moderate	High
Weight gain	High	High	High	Moderate	Moderate	Moderate	Low
Skin reactions							
Photosensitivity	Moderate	Low	Moderate	Low	Low	Low	Low

Note. ECG = electrocardiogram.

*Mesoridazine is no longer available in the United States.

	Phenothiazines						**Butyrophenone**
	Chlorpromazine	**Mesoridazine***	**Thioridazine**	**Fluphenazine**	**Perphenazine**	**Trifluoperazine**	**Haloperidol**
Rashes	Moderate	Low	Moderate	Low	Low	Low	Low
Pigmentation	High	Low	Low	Low	Low	Low	Low
Ocular effects							
Lenticular pigmentation	Low	Low	Low	Low	Low	Low	Low
Pigmentary retinopathy	Low	Low	Moderate	Low	Low	Low	Low
Other effects							
Blood dyscrasias	Low to moderate	Low	Low	Low	Low	Low	Low
Hepatic disorder	Low	Low	Low	Low	Low	Low	Low
Seizures	Moderate	Moderate	Moderate	Low	Low	Low	Low

Note. ECG = electrocardiogram.

*Mesoridazine is no longer available in the United States.

Cognitive Side Effects

CNS side effects of the classic antipsychotics can be subclassified into cognitive and neuromuscular side effects. Cognitive effects include sedation, confusion, disturbed concentration, memory impairment, and delirium (Himelhoch *et al.* 1996). Antihistaminergic and anticholinergic actions lead to sedation and slowed mentation. These effects, which are most pronounced with lower-potency agents (e.g., chlorpromazine), are most severe earlier in treatment, with some tolerance developing over time. Anticholinergic delirium is the most common cause of medication-induced delirium. Because delirium is associated with high rates of morbidity and mortality (> 20% mortality), this potential side effect is important, especially for individuals who are more sensitive to anticholinergic medications, such as older adults. In addition, every antipsychotic--but especially the low-potency agents--can potentially lower the seizure threshold.

Extrapyramidal Side Effects

Neuromuscular CNS side effects are due to antagonism of D_2 receptors in the nigrostriatal dopaminergic pathway. Generally, antipsychotics manifest EPS when dopaminergic blockade exceeds 75% of D_2 receptors. EPS are most common with the high-potency agents such as haloperidol. A greater risk of EPS differentiates the classic from the atypical antipsychotics; in fact, the term *atypical* was originally coined to highlight this ability to produce an antipsychotic effect equivalent to that of the typical high-potency agents with lower potential for EPS.

Acute-Onset EPS

Acute-onset EPS include medication-induced parkinsonism, acute dystonia, and akathisia. *Antipsychotic-induced parkinsonism* occurs in 15% of patients after several weeks of treatment. It is more common in patients older than 40 years, although it can occur at any age. Symptoms are identical to those of Parkinson's disease and include muscle stiffness (lead-pipe rigidity), cogwheel rigidity, shuffling gait, stooped posture, drooling, bradykinesia, resting tremor, masked facies, and akinesia. Slow, restricted movements of the body and face (akinesia) may be mistakenly diagnosed as being due to depression or the negative symptoms of schizophrenia.

It is estimated that up to 10% of patients may experience an acute dystonic episode, which usually occurs within the first few hours or days of treatment. It is more common in youths, in recent cocaine users, and with intramuscular doses of high-potency antipsychotics. Dystonia is an acute, sustained, painful muscular contraction. Potential areas of involvement include the tongue (protrusions, twisting), jaw, neck (spasmodic retrocollis or torticollis), and back (opisthotonos). If the dystonia involves the eyes, it results in a symmetrical or unilateral upward lateral movement called an oculogyric crisis. Laryngeal dystonia can result in sudden death secondary to a patient's inability to breathe. Dystonia can be extremely uncomfortable and frightening for patients and can lead to noncompliance with medication for fear of recurrence. Treatment of dystonia requires rapid diagnosis and intravenous administration of antihistaminergic or anticholinergic agents. Anticholinergic agents are often initiated with high-potency antipsychotics in an effort to avoid this side effect.

Akathisia is a subjective feeling of motor restlessness in which patients feel an irresistible urge to move continuously. It is described as an unpleasant sensation and may result in dysphoria. Akathisia can occur at any time during treatment and is the most prevalent EPS. It often leads to noncompliance with medications and is believed to increase suicide risk in some patients.

Late-Onset EPS

Tardive dyskinesia is characterized by a persistent syndrome of involuntary choreoathetoid movements of the head, limbs, and trunk. It generally takes at least 3 months of exposure to antipsychotics before the disorder develops. Perioral movements involving buccolingual masticatory musculature are the most common early manifestation of tardive dyskinesia. Tardive dyskinesia has an estimated yearly incidence of 5% among adults and as high as 25% in older adults who receive continuous conventional antipsychotic therapy, and it has been a major source of litigation in past psychiatric practice. The risk of developing tardive dyskinesia is reported to increase with age and to be higher in certain ethnic groups; female gender, presence of mood disorders, and early onset of EPS have also been associated with increased risk of tardive dyskinesia.

Tardive dyskinesia may be masked by continuing dopamine blockade and has a variable course following development. Over time, spontaneous resolution or improvement has been described in some patients. There is no single effective treatment, although treatment with clozapine has been reported to improve symptoms. Cases of tardive dyskinesia have been described with every antipsychotic, although classic antipsychotics are associated with a much greater risk of tardive dyskinesia than second-generation or atypical agents (Correll *et al.* 2004). Other tardive syndromes include tardive dystonia, tardive akathisia, and tardive pain.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a poorly understood syndrome that usually appears within hours or days of initiation of antipsychotic treatment. This syndrome is characterized by muscular rigidity, hyperpyrexia, autonomic instability

(hypotension or hypertension, tachycardia, diaphoresis, pallor), and altered consciousness. NMS has an estimated incidence of 0.02%-2% and carries a mortality rate of 20%-30%. Death most often occurs secondary to dysrhythmias, renal failure secondary to rhabdomyolysis, aspiration pneumonia, or respiratory failure. Laboratory findings include elevated creatine phosphokinase, elevated white blood cell (WBC) count, elevated liver enzymes, myoglobinemia, and myoglobinuria. The syndrome can last up to 14 days.

Treatment requires immediate discontinuation of the offending antipsychotic and supportive care with aggressive intravenous hydration. In the past, mild cases of NMS were treated with intravenous bromocriptine, and more severe cases were treated with intravenous dantrolene. However, randomized controlled clinical trials of NMS treatment have never been performed because of its infrequent occurrence.

Cardiac Effects

a-Adrenergic antagonism is associated with orthostatic hypotension with reflex tachycardia, with tolerance possibly developing later in the treatment course. Orthostasis is important because of an increase in falls and related injuries.

Recent studies involving several antipsychotics have drawn attention to the risk of cardiac dysrhythmias, which is especially prominent with use of lower-potency conventional antipsychotics. High dosage, rapid titration, intramuscular administration, and especially intravenous administration may be associated with a lengthening of the QTc interval, with a resulting risk of serious dysrhythmias such as torsades de pointes and ventricular fibrillation. Studies with thioridazine have raised concerns about piperidine antipsychotics, leading to a decrease in the use of this class. In reality, torsades de pointes is rarely encountered during treatment with conventional antipsychotics, although some have speculated that a syndrome of unexplained sudden death described with all conventional antipsychotics may be related to sudden dysrhythmias.

Gastrointestinal Side Effects

The anticholinergic actions of conventional agents include dry mouth, nausea, vomiting, and constipation that can progress to paralytic ileus. Antihistaminergic action is associated with medication-related weight gain.

Cholestatic jaundice is a hypersensitivity reaction described with the aliphatic phenothiazines, especially chlorpromazine (incidence of 0.1%). This reaction typically manifests during the first 1-2 months of treatment and presents with nausea, malaise, fever, pruritus, abdominal pain, and jaundice, with resulting elevations in levels of bilirubin and alkaline phosphatase. This condition rarely lasts > 2 weeks after discontinuation.

Weight Gain, Diabetes Mellitus, and Dyslipidemia

With the introduction of atypical antipsychotics, several of which cause significant weight gain, there is renewed awareness of the metabolic side effects associated with antipsychotic therapy such as obesity, elevated cholesterol and triglyceride levels, and an increased risk of diabetes mellitus. These metabolic changes increase the risk of ischemic heart disease and contribute to the increased mortality observed in

schizophrenia. Antihistaminergic action is associated with medication-related weight gain, which greatly increases the patient's risk of developing diabetes. Diabetes is currently described as a worldwide epidemic. Serotonin 5-HT_{2C} receptor blockade also significantly contributes to weight gain (Tandon and Halbreich 2003). There are significant differences between classic antipsychotics with reference to their propensity to cause these metabolic adverse effects. Molindone is the least likely to cause weight gain, whereas thioridazine and chlorpromazine are among the most likely to do so. In general, high-potency agents cause less weight gain than do low-potency agents.

Genitourinary Side Effects

Renal effects secondary to blockade of M_1 receptors include urinary hesitancy or retention, which can lead to a comparable increase in urinary tract infections in both sexes. As mentioned previously, antagonism of tuberoinfundibular dopaminergic tracts increases prolactin secretion. Clinical manifestations of hyperprolactinemia include gynecomastia, galactorrhea, diminished libido, erectile dysfunction, amenorrhea, decreased bone density, menstrual irregularities, infertility, delayed ovulation, and possibly increased risk of breast cancer. Other sexual side effects, such as erectile disorder, retrograde ejaculation (due to blockade of a_2-adrenergic receptors), anorgasmia, and occasionally priapism, can also occur with conventional antipsychotics.

Hematological Side Effects

Hematological effects of conventional antipsychotics include transient leukopenia (WBC count < 3,500/mm^3), which is common but not usually problematic, and agranulocytosis (WBC count < 500/mm^3), a life-threatening problem. Agranulocytosis occurs most often during the first 3 months of treatment, with an incidence of 1 in 500,000. Aliphatic and piperidine phenothiazines are the most common causal agents among the conventional antipsychotics. Rarely, thrombocytopenic or nonthrombocytopenic purpura, hemolytic anemia, and pancytopenia may occur.

Ocular Side Effects

In addition to direct anticholinergic ocular effects such as blurred vision (mydriasis and cycloplegia) and exacerbation of open-angle glaucoma, direct optic toxicity has been described. The conventional antipsychotics are associated with several kinds of optical pathology involving the lens, cornea, and retina. Lenticular opacities have been reported with some phenothiazines, including perphenazine, chlorpromazine, and thioridazine. An irreversible increase in retinal pigmentation has been described with thioridazine when high dosages (> 800 mg/day) are used. This retinal pigmentation, which can progress even after drug discontinuation, can lead to reduced visual acuity and even blindness. Early symptoms include poor night vision and secondary nocturnal confusion.

Dermatological Side Effects

Cutaneous side effects of the conventional antipsychotics involve hypersensitivity rashes--most commonly maculopapular erythematous rashes of the trunk, face, neck, and extremities--and photosensitivity reactions that can lead to severe sunburn. Care must be taken with injectable versions of many antipsychotics because of the risk of direct dermatological toxicity if the skin or subcutaneous layers are exposed. Prolonged use of chlorpromazine can lead to blue-gray discoloration in body areas exposed to sunlight.

Neurotoxicity

Over the past 20 years, 32 studies published in neuroscience journals have reported on the neurotoxic effects of haloperidol and several other first-generation agents. These neurotoxic effects are mediated by 15 different molecular mechanisms (reviewed in Nasrallah and Chen 2017). A meta-analysis of 18 neuroimaging studies comparing FGAs and SGAs confirmed the finding of progressive atrophy of brain volume in individuals maintained on first-generation but not second-generation agents (Vita *et al.* 2015). In our opinion, those studies should prompt clinicians to avoid use of the FGAs and instead to use one of the SGAs, which as a class have been demonstrated to have at least 24 different neuroprotective effects in the brains of patients receiving them (reviewed by Chen and Nasrallah 2019).

Drug-Drug Interactions

Careful consideration should be given to a patient's existing drug regimen before the initiation of antipsychotic therapy.

Protein Binding

Because conventional antipsychotics are tightly protein bound, care must be taken when these medications are administered with other highly protein-bound medications. Mutual displacement of medications such as phenytoin, digoxin, warfarin, and valproate could lead to a short-term increase in serum levels of these drugs and of the conventional antipsychotic. However, protein binding has not been of serious clinical significance.

CYP Inhibition

As mentioned previously, conventional antipsychotics are primarily hepatically metabolized through the CYP2D6 and 3A4 enzymes. In addition, each inhibits the 2D6 enzyme to some degree. Care must be taken when conventional agents are coadministered with potent CYP2D6 inhibitors such as fluoxetine, paroxetine, cimetidine, erythromycin, and certain class IC antiarrhythmics (e.g., quinidine). Similarly, potent CYP3A4 inhibitors such as nefazodone, fluvoxamine, and ketoconazole should be used with care. Inhibitors of CYP2D6 and 3A4, as well as competitive substrates, should be used carefully with conventional antipsychotics because of their potential to increase plasma levels. CYP1A2, induced by nicotine and inhibited by estrogen, plays a role in metabolizing some antipsychotics.

Conclusion

The classic antipsychotics revolutionized the practice of psychiatry and the treatment of patients with severe mental illness throughout the world. Second-generation

"atypical" antipsychotics have commercially eclipsed these first-generation agents to a large extent, such that more than 90% of patients with schizophrenia and related psychoses in the United States are currently receiving one of the atypical oral agents. In regard to long-acting (depot) agents, second-generation injectable agents are gradually displacing classic antipsychotic injectables such as haloperidol decanoate and fluphenazine decanoate. The landmark National Institute of Mental Health-funded CATIE study, which compared four SGA oral agents (olanzapine, quetiapine, risperidone, and ziprasidone) against one FGA oral agent (perphenazine), showed that there was no difference between the two generations in clinical effectiveness (defined as time to all-cause treatment discontinuation) (Lieberman *et al.* 2005). However, the CATIE study excluded subjects with tardive dyskinesia from random assignment to perphenazine and instead assigned them to one of the atypical agents. This methodological stipulation may have confounded the findings, because the 231 subjects with tardive dyskinesia were later found to have a higher severity of psychopathology and a much greater likelihood of substance use (Nasrallah 2006). Additionally, the subjects' low propensity to develop EPS led to a ceiling effect finding of no EPS differences between perphenazine and the SGAs. Nonetheless, both classic antipsychotics and atypical antipsychotics can cause serious side effects, with neurological adverse events being much more likely with the FGAs and metabolic complications being more common with the SGAs.

Conventional antipsychotics will always be remembered for their critical role as the foundation of antipsychotic pharmacotherapy and as the main impetus for the remarkable neuropharmacological progress in psychiatric neuroscience over the second half of the twentieth century. They retain an important, if limited, role in the antipsychotic armamentarium of the twenty-first century.

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CHAPTER 26

Clozapine

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History and Discovery

Clozapine has played a critical role in the history of therapeutics for psychosis. When clozapine was initially developed in the 1960s (following its synthesis in 1958 in Switzerland), there was skepticism as to whether an agent that barely caused catalepsy in rodents could be an effective antipsychotic. According to Hippius (1999), there was limited enthusiasm for this drug because its profile was inconsistent with the "neuroleptic dogma" that extrapyramidal side effects (EPS) were an essential feature of an antipsychotic agent. Nevertheless, Hippius and others challenged this dogma and supported clozapine's development in Germany. As a result, clozapine was eventually marketed in several countries in Europe.

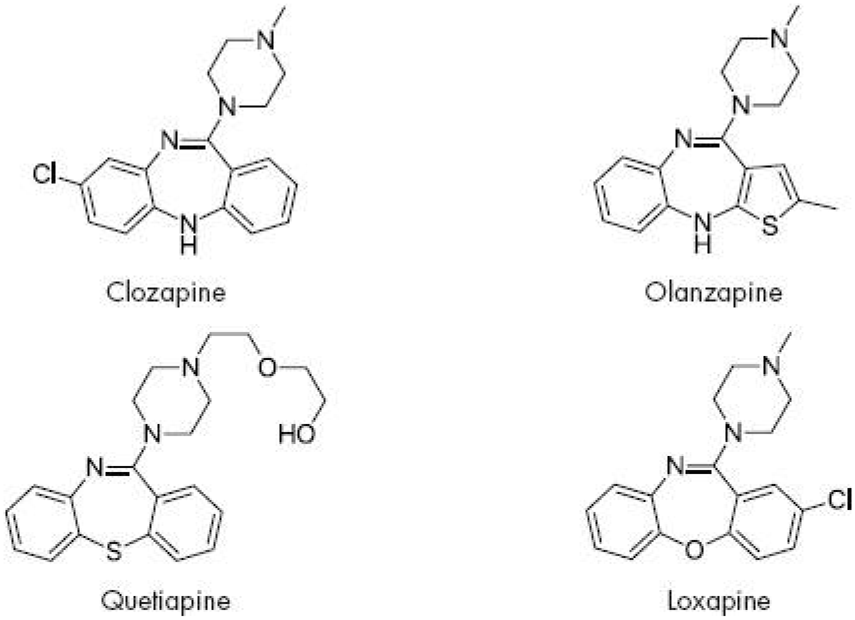
Enthusiasm about clozapine's unique profile evaporated when it was reported that 13 patients in Finland developed agranulocytosis during treatment with clozapine and that 8 of these patients died (Griffith and Saameli 1975). This news led to a near-halt in research on clozapine, and in the United States, clozapine's investigational new drug application came to a halt. However, attempts to switch patients to other antipsychotic agents resulted in substantial deterioration in some individuals (Hippius 1999). Some of these patients were switched back to clozapine and were carefully monitored with regular white blood cell (WBC) counts. Thus, it was found that if clozapine was discontinued, the agranulocytosis reversed and the drug could be readministered safely (Honigfeld *et al.* 1998). Moreover, studies revealed that clozapine was particularly effective for patients who were severely ill and for those who had failed to respond to treatment with conventional antipsychotics. After a series of stops and starts, clozapine was finally demonstrated to have superiority over chlorpromazine for treatment-resistant schizophrenia and was approved by the FDA in 1990 (Crilly 2007; Iqbal *et al.* 2003; Kane *et al.* 1988).

The discovery that clozapine was an effective antipsychotic that caused minimal EPS led to a reassessment of the reigning models of the antipsychotic effect. The exact mechanism of clozapine's antipsychotic action was and remains unknown. However, its greater

efficacy than first-generation antipsychotics (FGAs) led to the development of the second-generation antipsychotics, or SGAs. Attempts to understand clozapine's mechanism of action have raised more questions than answers in our understanding of the physiology and pharmacology of schizophrenia, yet it remains the most effective antipsychotic.

Structure-Activity Relationships

Clozapine, or 3-chloro-6-(4-methylpiperazin-1-yl)-5*H*-benzo[b][1,4]benzodiazepine (National Center for Biotechnology Information 2022a, 2022d), belongs to the group of tricyclic antipsychotics known as the dibenzazepines. This group is characterized by a seven-member dibenzazepine central ring substituted with oxygen, nitrogen, sulfur, or carbon (Iskra and Decker 2012). The antipsychotic dibenzepines include a loxapine-like group of compounds (the dibenzoxazepines) and a clozapine-like group (the dibenzodiazepines). The structures of clozapine and its derivatives olanzapine and quetiapine can be seen in Figure 26-1. Interestingly, the structure of the FGA antipsychotic loxapine is quite similar to that of clozapine (National Center for Biotechnology Information 2022a, 2022b, 2022c), with only two substitutions distinguishing them.



Clozapine

Olanzapine

Quetiapine

Loxapine

FIGURE 26-1. Chemical structures of clozapine, olanzapine, quetiapine, and loxapine. Olanzapine and quetiapine were based on clozapine's chemical structure, and their similarities can be seen clearly here. It is also striking how similar the structure of loxapine, a typical antipsychotic, is to that of clozapine, the prototypical atypical antipsychotic.

Source. Adapted from PubChem Compound Database, National Center for Biotechnology Information (https://pubchem.ncbi.nlm.nih.gov/pccompound).

Clozapine is also known to be a fast-off dopamine$_2$ (D_2) receptor antagonist, with a rapid disassociation time of less than 1 minute for 50% binding of D_2 receptors (Seeman 2014). Tresadern *et al.* (2011) examined more than 1,800 compounds and found that "increased hydrophilicity, increased number of nitrogen atoms, lower MW [molecular weight], fewer rings, less chiral centers, and increased partial positive charge all contribute to a faster dissociation from the D_2 receptor" (p. 27).

Pharmacological Profile

To quote Wenthur and Lindsley (2013), "clozapine is a broad spectrum ligand" because it binds to more receptors than perhaps any molecule in psychopharmacology (Stahl 2013). Clozapine and the other SGAs are often identified through their equal or greater antagonism of the serotonin$_{2A}$ (5-

HT_{2A}) receptor compared with their D_2 receptor antagonism. However, clozapine in fact binds to more than 20 receptors more strongly than in toes to the D_2 receptor and to at least four receptors equally or more strongly than to the 5-HT_{2A} receptor (Stahl 2013; Wenthur and Lindsley 2013). Of all the antipsychotics, quetiapine, whose structure was based on that of clozapine, is most similar in pharmacological profile to clozapine.

Dopamine Receptors

Clozapine is a D_2 antagonist that binds D_2 receptors approximately 50-100 times more weakly than haloperidol and 10 times more weakly than chlorpromazine (Ashby and Wang 1996). At therapeutic concentrations, clozapine occupies only 40%[?]60% of D_2 receptors, in contrast to most FGAs, which occupy more than 80% of D_2 receptors (Wenthur and Lindsley 2013). Clozapine binds less tightly to D_2 receptors than to dopamine itself and may be displaced by endogenous dopamine (Seeman 2014). It also has equivalent occupancy of $dopamine_1$ (D_1) and D_2 receptors at therapeutic dosages (Tauscher *et al.* 2004). In order, clozapine binds most strongly to $dopamine_4$ (D_4) > D_1 > $dopamine_5$ (D_5) > D_2 > $dopamine_3$ (D_3) receptors (Wenthur and Lindsley 2013).

Serotonin Receptors

Clozapine binds to and antagonizes 5-HT_{2A}, $serotonin_{2B}$ (5-HT_{2B}), and $serotonin_{2C}$ (5-HT_{2C}) receptors 15-30 times more strongly than it does D_2 receptors (Stahl 2013; Wenthur and Lindsley 2013). Clozapine also has high affinity for $serotonin_5$ (5-HT_5) receptors and acts as a partial agonist at $serotonin_{1A}$ (5-HT_{1A}) receptors.

Muscarinic Receptors

Clozapine binds strongly to muscarinic acetylcholine receptors $M_{1\text{-}5}$, with varying of partial agonist versus competitive antagonist activity, depending on the cell line studied (Foster *et al.* 2021). Clozapine's high affinity for muscarinic receptors likely causes many of its well-known side effects, such as sedation, constipation, and the dangerous complication of ileus.

Adrenergic Receptors

Clozapine binds strongly to a_1-adrenergic receptors in the CNS, based on PET studies of ^{3}H-prazosin binding displacement in animal models (Ashby and Wang 1996). Clozapine's a_1-adrenergic receptor antagonism likely contributes to its sedative properties and also to some of its cardiac side effects, including orthostatic hypotension and tachycardia.

Histamine Receptors

Clozapine binds very strongly to histamine$_1$ (H_1) receptors. This likely contributes to its associated sedation and increases in patients' appetite and weight, possibly leading to

diabetes and metabolic syndrome. Preliminary research has been done on histamine agonists to counteract the metabolic effects of SGAs; however, no well-powered, placebo-controlled randomized trials have been performed (Poyurovsky *et al.* 2005).

Glutamate Receptors

Although clozapine does not bind directly to glutamate receptors, it has been shown to inhibit the reuptake of glycine at the synapse in rats, resulting in increased glycine at the synapse and thus increased *N*-methyl-D-aspartate (NMDA) receptor signaling (Javitt *et al.* 2005). Moreover, clozapine's main metabolite, *N*-desmethylclozapine (NDMC), or norclozapine, is an M_1 agonist known to increase NMDA receptor activity (Wenthur and Lindsley 2013).

GABA Receptors

It is hypothesized that clozapine may act on the $GABA_B$ receptor, although thus far direct evidence of binding to GABA receptors has not been observed (Nair *et al.* 2020). Animal behavioral models have been of limited use in schizophrenia due to a lack of well-accepted animal models of psychopathology in schizophrenia. The reasons for this are numerous. First, the high level of complexity of both the contributions of genetics to psychosis and of the symptom domains of psychosis means that a model can only represent part of a psychotic disorder. Second, the subjective quality of many psychotic experiences, such as paranoia, hallucinations, and delusions, make these symptoms and experiences difficult to measure in animals. Third, the human brain is many times more complex than even that of a monkey, not to mention that of a rodent, as evidenced by the large number of folds in the human brain and the complete absence of folds in the rodent brain. Finally, terms such as *schizophrenia* and *psychosis* continue to function as umbrella terms for what is likely numerous diseases presenting with overlapping symptoms and syndromes, making differentiation of one illness from another difficult in humans, and far more so in animal models.

That said, a number of animal models--including prepulse inhibition (PPI), latent inhibition (LI) of the conditioned response, and the conditioned avoidance response (CAR)--are being studied from a more reductionist standpoint. PPI is a sensory gating phenomenon thought to relate to the relative difficulty patients with schizophrenia have with separating salient information from non-salient information in the environment. These models are being seen less as complete models of the disease than as models of specific neurophysiological aspects of psychosis that can inform us about particular characteristics of the illness (Wong and Josselyn 2016), and they suggest unique properties of clozapine. For instance, as reviewed by Geyer *et al.* (2001), deficits in PPI induced by NMDA receptor antagonists were most likely to respond to clozapine-like SGAs and not to FGAs.

Pharmacokinetics and Disposition

Clozapine is readily orally absorbed, and tablets and suspension have equivalent bioavailability. However, due to extensive first-pass metabolism, its absolute oral bioavailability is only about 50%. Peak plasma levels are reached approximately 2 hours after oral administration. The elimination half-life at steady state is about 12 hours, and patients usually reach steady-state plasma concentrations within 5-7 days (HLS Therapeutics 2023). The coadministration of highly protein-bound drugs may lead to increased free clozapine levels, although the total (free plus bound) levels may be unchanged. Clozapine's volume of distribution is lower than that of other antipsychotic drugs but is nonetheless large, with a mean of 2.0-5.1 L/kg (range 1.0-10.2 L/kg). Clozapine easily crosses the blood-brain barrier.

As mentioned, clozapine undergoes extensive first-pass metabolism in the liver and gut. Although it is predominantly metabolized by cytochrome P450 (CYP) 1A2, CYP2D6 and CYP3A3/4 also contribute (Buur-Rasmussen and Brosen 1999; Wenthur and Lindsley 2013). Plasma concentrations of clozapine average about 10-80 ng/mL per milligram of drug given per kilogram of patient weight. Thus, a typical daily dosage of 300-400 mg (about 5 mg/kg) is associated with plasma levels ranging from 200 to 400 ng/mL. However, there is considerable variability among individuals treated with clozapine. Several studies have focused on the clinical implications of this variation, and, when taken together, they indicate that patients are more likely to do well when their plasma levels are greater than 350 ng/mL (Bell *et al.* 1998; Kronig *et al.* 1995; Miller 1996; Miller *et al.* 1994; Potkin *et al.* 1994). If patients have not responded after 6 weeks with a plasma level of 250 ng/mL, the clinician should increase the level to approximately 350 ng/mL. High levels, such as 600 ng/mL, are not associated with a greater likelihood of improvement than moderate levels and may be associated with a higher incidence of side effects, including increased seizure risk. Therefore, patients with high levels and side effects may benefit from having the dosage reduced.

When interpreting plasma concentrations of clozapine, clinicians should consider whether the laboratory is reporting just the parent drug or clozapine plus norclozapine. If the latter, levels will be higher. Generally, the clozapine : norclozapine ratio is between 1.5 and 2; if higher than 3, this may indicate that the clozapine level does not reflect a trough level, whereas if the ratio is less than 1.5, this could indicate saturation and low utility of a higher dose (Couchman *et al.* 2010). A lower ratio may also be associated with better cognitive performance (Costa-Dookhan *et al.* 2020). In general, however, decisions about clozapine dose should be made based on assessment of clinical and side effects, not clozapine level.

Pharmacogenetic Profile

In recent years, several studies have linked genetic polymorphisms to either response to clozapine or the likelihood of experiencing side effects, such as weight gain and clozapine-induced agranulocytosis (CIA). The most important of these are single-nucleotide polymorphisms in human leukocyte antigen *(HLA)-DQB1* and *HLA-B* associated with CIA (Goldstein *et al.* 2014). CYP genetic variants have been associated with decreased response to clozapine, and polymorphisms in the gene for brain-derived neurotrophic factor (*BDNF*) have been found to be associated with improved response (Sriretnakumar *et al.* 2015). The Pro12Ala polymorphism of the peroxisome proliferator-activated receptor gene g2 (*PPAR*-g2) appears to predispose patients on clozapine to metabolic syndrome: patients with the Pro-Ala substitution had a 53.8% likelihood of having metabolic syndrome, whereas those with the Pro-Pro polymorphism had only a 16.3% likelihood (Fernandez *et al.* 2012). However, none of these findings has produced a

clinically useful pharmacogenomics tool for clinicians (Islam *et al.* 2021). Although not yet integrated into clinical practice, the pharmacogenetics of clozapine may soon help inform clinicians about the likelihood of a patient either responding to clozapine treatment or developing a concerning side effect.

Mechanism of Action

The effectiveness of antipsychotics was previously thought to be solely associated with D_2 receptor blockade, and induction of EPS was thought to be necessary for antipsychotic action. Clozapine's low rates of EPS but superior efficacy as an antipsychotic undermined and eventually overturned these ideas. The exact mechanism of clozapine's antipsychotic effect remains unknown, but several theories have been proposed. In the following discussion we describe the possible mechanisms of both clozapine's low EPS and its highly effective antipsychotic effect.

Dual 5-HT_{2A}/D_2 Antagonism

The low level of EPS from clozapine treatment (and many other SGAs) was thought to be due to its greater activity at the 5-HT_{2A} receptor than at the D_2 receptor (Meltzer and Massey 2011; Meltzer *et al.* 1989, 2003). This model, as laid out by Stahl (2013), is as follows: D_2 receptor antagonism in the mesolimbic pathway (projecting from the midbrain ventral tegmental area to the nucleus accumbens) reduces excessive dopamine signaling in the nucleus accumbens and reduces positive symptoms. However, D_2 receptor antagonism of the nigrostriatal pathway, which projects from the substantia nigra to the striatum of the basal ganglia, causes Parkinson-like involuntary movements, dystonias, and other EPS. Clozapine's antagonism of the 5-HT_{2A} receptor in the striatum results in increased local release of D_2, which results in relief from the EPS caused by D_2 antagonism. Similarly, in the tuberoinfundibular tract, which projects from the hypothalamus to the anterior pituitary gland, D_2 antagonism causes increased prolactin secretion, resulting in gynecomastia, galactorrhea, amenorrhea, and decreased libido. Local 5-HT_{2A} antagonism at the pituitary gland from SGAs increases local D_2 signaling and thus reverses the increase in prolactin secretion.

Although this characteristic of the SGAs may be associated with their relatively lower rates of EPS compared with FGAs, some evidence calls this into question. For instance, risperidone has high affinity for 5-HT_{2A} receptors yet also has high rates of gynecomastia and galactorrhea. Also, quetiapine produces very few EPS but has no specificity for 5-HT_{2A} receptors.

Low Percentage of D_2 Receptor Occupancy

Clozapine and some other SGAs have been shown to occupy less than 60% of D_2 receptors at therapeutic doses, in contrast to 75%-80% binding with the FGA class. This may explain the low rate of EPS with most SGAs.

Fast-Off D_2 Receptor Dissociation

Kapur and Seeman (2001) and others have proposed that the rapid dissociation of clozapine from the D_2 receptor could give rise to its low EPS and efficacy for psychosis. This fast dissociation or "loose binding" characteristic allows clozapine to be displaced by endogenous dopamine, thus allowing more physiological signaling than during treatment with most other antipsychotics. In their review, Kapur and Seeman noted that if D_2 receptor occupancy was high, EPS occurred even in the presence of strong 5-HT_{2A} antagonism, whereas rapid dissociation from the D_2 receptor in in vitro studies had the closest correlation with "atypicality."

Clozapine's Exceptional Efficacy

To date, clozapine remains the most effective antipsychotic in the clinician's arsenal. What could explain clozapine's superior efficacy? Let us examine two very similar antipsychotics, clozapine and its derivative, quetiapine. Clozapine and quetiapine have very similar pharmacological profiles, have the highest dissociation constants from the D_2 receptor, have fast-off dynamics at the D_2 receptor, and have high binding affinity to the 5-HT_{2A} receptor. However, the antipsychotic efficacy of quetiapine cannot match that of clozapine (McEvoy *et al.* 2006). What can explain clozapine's superior efficacy to all other antipsychotics? This remains one of the ongoing mysteries of treatment of schizophrenia. A few theories are discussed in the following subsections.

D_1:D_2 Equivalent Occupancy

The differences in efficacy between clozapine and quetiapine despite their similarities could be explained by the differential D_1:D_2 occupancy ratio between clozapine and other members of the SGA class. In a PET study using ^{11}C-SCH23390 and ^{11}C-raclopride to determine D_1 and D_2 receptor occupancy in patients with schizophrenia, clozapine was found to have the highest D_1:D_2 receptor occupancy ratio (0.88), compared with olanzapine (0.54), quetiapine (0.41), and risperidone (0.31) (Tauscher *et al.* 2004).

D_4 Receptor Binding

Clozapine also has a very high affinity for the D_4 receptor, which is widely distributed in the cortex and less so in striatal areas. It was thought that this D_4 binding could be the unique characteristic that gives clozapine its superior efficacy against psychosis. However, other agents with high D_4 receptor activity have failed to demonstrate antipsychotic activity.

Combination of Activity at Multiple Specific Receptor Types

None of the theories discussed thus far can explain the unique efficacy of clozapine for psychosis. Another possibility is that the unique signature of clozapine's receptor binding profile among the dopaminergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors explains its unique efficacy. Clozapine may also have unknown activity at other receptors, such as glutamate, GABA, and neuropeptide receptors.

Metabolites

Clozapine's primary metabolite, norclozapine, is thought to possibly have a role in its antipsychotic effect because the metabolite represents 10%-90% of circulating active drug in patient serum (Wenthur and Lindsley 2013). However, trials of norclozapine have not demonstrated antipsychotic efficacy.

Indications and Efficacy

Acute Schizophrenia and Schizoaffective Disorder

Because of its side-effect profile, clozapine should not be administered as a first-line agent for schizophrenia or schizoaffective disorder. However, it remains the most effective antipsychotic available for treatment of schizophrenia and schizoaffective disorder. In a recent systematic quantitative meta-review of 112 meta-analyses, clozapine was found to be superior to FGAs and SGAs with regard to symptoms, relapse, hospitalization, mortality, and all-cause discontinuation (Wagner *et al.* 2021). This is consistent with numerous other studies, including large registry studies, indicating that clozapine surpasses all other oral antipsychotics in its efficacy (Tiihonen *et al.* 2017).

Treatment-Refractory Schizophrenia

Early studies suggested that clozapine was particularly effective in patients with more severe treatment-refractory forms of schizophrenia. This was important when it was discovered that clozapine was associated with a risk of agranulocytosis. Given that clozapine was viewed as an agent that might be helpful for patients who had failed to respond to other antipsychotics, a study was designed to test whether it could play a role in treatment of this population. As a result, a multicenter study was designed that compared clozapine with chlorpromazine in severely ill patients with treatment-refractory schizophrenia (Kane *et al.* 1988). Treatment-refractory illness was characterized based on the patient's history of drug non-responsiveness and failure to improve during a 6-week trial of up to 60 mg of haloperidol. Clozapine resulted in greater improvement in nearly every dimension of psychopathology. Thirty percent of the patients treated with clozapine met stringent improvement criteria, compared with only 4% of those treated with chlorpromazine. Other studies have suggested that the proportion of patients improving with clozapine treatment will be higher if clozapine is continued for a longer time. For example, a 16-week trial by Pickar *et al.* (1992) found a 38% improvement rate. A more recent report (Kane *et al.* 2001) found that 60% of patients with treatment-refractory illness improved after a 29-week trial on clozapine.

Two large trials compared clozapine with SGAs in individuals who had treatment-resistant illness. In the United States, the National Institute of

Mental Health's Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) compared clozapine with risperidone, olanzapine, or quetiapine in patients with schizophrenia who had failed to show response in an earlier phase of the study because of a lack of efficacy (Stroup *et al.* 2006). Clozapine was administered open label, whereas the other antipsychotics were administered double-blind. Patients assigned to clozapine had the lowest discontinuation rates, with 56% of patients taking clozapine discontinuing treatment, compared with 71% of those taking olanzapine, 86% of those taking risperidone, and 93% of those taking quetiapine. Clozapine-treated patients also showed greater symptom improvements than those receiving the other agents. A trial in the United Kingdom, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study-Band 2 (CUtLASS-2; Lewis *et al.* 2006), randomly assigned 136 patients who had responded poorly to two prior antipsychotics to either clozapine or an SGA selected

prior to randomization. Patients who received clozapine demonstrated greater improvement than those who received the comparison drugs.

Treatment-resistant schizophrenia is now generally agreed to mean schizophrenia that has failed to respond to two antipsychotic trials of sufficient dosage and duration (Correll and Howes 2021). A large body of evidence indicates that clozapine has an important role in the treatment of patients whose illness has failed to respond to either FGAs or other SGAs. Clozapine's advantages are clearest in patients whose illness failed to respond to FGAs but are still apparent in those whose illness responded inadequately to other SGAs. Because clozapine is associated with a risk of agranulocytosis and other side effects (summarized later in this chapter in the section "Side Effects and Toxicology"), patients should probably receive a trial of two other antipsychotics, one of which is an SGA, before receiving a trial of clozapine (Lehman *et al.* 2004a, 2004b; Marder *et al.* 2002; Miller *et al.* 2004).

Hostile and Aggressive Behavior in Schizophrenia

Clozapine may have other advantages for patients with schizophrenia. Several studies suggest that clozapine may decrease hostility and aggression more effectively than other agents. In a study of 157 inpatients (Citrome *et al.* 2001), clozapine produced greater reductions in scores on the hostility item from the Positive and Negative Syndrome Scale (PANSS) than did the FGAs and other SGAs. A study by Chengappa *et al.* (2003) found significant reductions in the rates of seclusion and restraint among patients with schizophrenia who had received clozapine during the first 3 years after its introduction. Other randomized studies have consistently found that patients treated with clozapine exhibit less hostility and less aggressive behavior than patients given comparator agents (Essock *et al.* 2000; Kane *et al.* 1988). A 2021 study of patients with a history of physical assaults and schizophrenia found that clozapine was more effective than olanzapine and haloperidol at reducing assaults (Krakowski *et al.* 2021). A 2020 study from Sweden found that clozapine was associated with a lower rate of violent offending than olanzapine (Bhavsar *et al.* 2020). These findings suggest that clozapine may be of particular benefit to patients with treatment-refractory illness who demonstrate hostile and aggressive behavior.

Schizophrenia Patients at High Risk for Suicide

Clozapine may also be a preferred agent for patients with schizophrenia who are at a higher risk for suicide. Large epidemiological studies have found that mortality from suicide is reduced among individuals taking clozapine (Reid *et al.* 1998; Walker *et al.* 1997). Meltzer and Okayli (1995) followed patients whose treatment was changed to clozapine and found a reduction in the number of serious suicide attempts as well as in expressed depression and hopelessness. Another convincing study was a comparison of clozapine and olanzapine in 980 patients with schizophrenia who were considered to be at risk for suicide. In that study, clozapine was more effective than olanzapine in reducing the risk of suicide (Meltzer 2002). In a Finnish study, SGAs were associated with decreased mortality from suicide in first-episode patients, whereas FGAs were associated with increased mortality. When clozapine, olanzapine, quetiapine, and risperidone were compared, only clozapine was found to have a strong anti-suicide effect (Kiviniemi *et al.* 2013).

Schizophrenia With Comorbid Substance Abuse

Although the effectiveness of clozapine in patients with comorbid substance abuse has not been demonstrated in randomized controlled trials, there is some supporting evidence from naturalistic studies. One retrospective study (Green *et al.* 2003) found that patients treated with clozapine were more likely than those treated with risperidone to abstain from alcohol and cannabis use. A prospective study (Green *et al.* 2007) found that patients treated with clozapine were often able to reduce their substance abuse. This finding was supported by other prospective studies (Brunette *et al.* 2006; Drake *et al.* 2000), indicating that clozapine is effective for reducing substance abuse.

Mania in Bipolar Disorder

Given that all available antipsychotics are effective in reducing manic symptoms, it is not surprising that clozapine is effective in bipolar mania. However, accumulating evidence suggests that clozapine is particularly effective for manic symptoms that are not responsive to other agents. McElroy *et al.* (1991) were among the first to observe clozapine's unique effects in patients with bipolar disorder. Subsequent studies have confirmed clozapine's effectiveness as monotherapy and as a supplementation medication for mania in bipolar disorder. In an open-label randomized trial in acutely manic patients (Barbini *et al.* 1997), clozapine was as effective as chlorpromazine and had a more rapid onset of action. Suppes *et al.* (1999) randomly assigned patients with treatment-resistant schizoaffective or bipolar illness to either supplemental clozapine or treatment as usual during a 1-year open-label trial. Among both groups of patients, those treated with clozapine demonstrated greater improvements.

Depression With Psychotic Features

Limited evidence suggests that clozapine is effective as monotherapy and as an adjunctive treatment for patients with major depressive disorder with psychotic features. This evidence is currently confined to case reports from relatively small numbers of cases (Ranjan and Meltzer 1996; Rothschild 1996).

Psychosis in Parkinson's Disease

Psychosis with delusions and hallucinations occurs in approximately 25% of patients with Parkinson's disease (Wolters and Berendse 2001). These symptoms frequently appear in patients who are receiving dopaminomimetic drugs but may also occur because of a cholinergic deficit. Three double-blind studies (The French Clozapine Parkinson Study Group 1999; Jones and Stoukides 1992; Parkinson Study Group 1999; Pollak *et al.* 2004) found that clozapine at dosages as low as 25-50 mg/day was effective in reducing psychotic symptoms. Moreover, these dosages were not associated with an increase in tremor and rigidity. A report from the American Academy of Neurology (Miyasaki *et al.* 2006) recommended clozapine as a preferred agent for psychosis in Parkinson's disease.

Schizophrenia in Children and Adolescents

A 2018 network meta-analysis found that clozapine was superior in efficacy to other antipsychotics for treatment of children and adolescents (Krause *et al.* 2018). It was also associated with substantial weight gain.

Augmentation Strategies in Partial Responders to Clozapine

Some studies have evaluated augmentation strategies for individuals who are partial responders to clozapine. A meta-analysis (Sommer *et al.* 2012) reviewed 29 double-blind randomized trials of agents used to augment the effects of clozapine. The most-studied antipsychotics added to clozapine were risperidone and aripiprazole, and the most-studied mood stabilizer was lamotrigine. Although some of the studies reported positive findings, none of the strategies was viewed as having adequate empirical support. Augmentation with electroconvulsive therapy (ECT) has been shown to be more promising, with a prospective, randomized study demonstrating a 50% response rate in clozapine-treated patients who received ECT, compared with 0% in those who remained on clozapine alone (Petrides *et* *al.* 2015). A survey among members of the Treatment Response and Resistance In Psychosis (TRRIP) working group reached consensus on recommending augmentation with ECT, amisulpride, or oral aripiprazole (Wagner *et al.* 2020).

Maintenance Therapy in Schizophrenia

Clozapine use has largely been confined to patients with treatment-refractory schizophrenia. As a result, clozapine has not been studied in traditional relapse prevention designs in which patients who are stable are randomly assigned to either clozapine or a comparator. Nevertheless, substantial data support clozapine's long-term effectiveness. Breier *et al.* (2000) evaluated the outcomes of 30 patients with schizophrenia who received clozapine for 1 year. Patients given clozapine experienced fewer relapses and rehospitalizations than they had in the year prior to being changed to clozapine. A study in the state hospitals in Connecticut compared patients who were assigned to clozapine with patients who were maintained on their usual antipsychotics (Essock *et al.* 2000). Although clozapine did not result in a greater likelihood of hospital discharge, patients who were treated with clozapine had a higher likelihood of remaining in the community following discharge. This finding supports the observation that clozapine is associated with a reduced risk of relapse compared with conventional antipsychotics.

A study from the U.S. Department of Veterans Affairs Cooperative Studies Program compared haloperidol and clozapine in patients with treatment-refractory schizophrenia (Rosenheck *et al.* 1997). This study was not designed as a relapse prevention trial but rather as a comparison of the two agents in individuals whose illness had responded poorly to conventional therapy. However, the 1-year study is somewhat informative about the usefulness of the two drugs in patients living in the community. Fifty-seven percent of the patients taking clozapine completed the study, compared with only 28% of the patients taking haloperidol ($P < 0.001$). Using 20% improvement on the PANSS as the criterion for response, the investigators found that 42% of patients treated with clozapine and 31% of patients treated with haloperidol were responders ($P = 0.09$). In addition, clozapine-treated patients had fewer mean days of hospitalization (143.8 days) compared with haloperidol-treated patients (168.1 days; $P = 0.03$).

Other Indications

Clozapine may also help patients with polydipsia-hyponatremia syndrome (Canuso and Goldman 1999). Patients with this syndrome tend to intoxicate themselves through excessive water drinking, and the resultant hyponatremia may result in seizures.

Clozapine has historically been used to treat tardive dyskinesia (TD), although it has not been formally studied extensively for this purpose. In a 1991 review, Lieberman *et al.* (1991) reviewed eight small studies and conducted their own study of 30 patients with TD and found that in 50% of patients, clozapine reduced TD symptoms by approximately 43% (Lieberman *et al.* 1991). Other studies found equivocal results; however, in no study did clozapine worsen TD. Kimiagar *et al.* (2012) found that TD symptoms were reversed with a combination of clozapine, clonazepam, and tetrabenazine. Clozapine's mechanism of action for reducing TD remains unknown.

Side Effects and Toxicology

Hematological Effects

The side effects of clozapine make it one of the most challenging medications for psychiatrists to prescribe. The main factor that limits its use is the potential serious side effect of CIA. *Agranulocytosis* is defined as a drop in absolute neutrophil count (ANC) to levels below 500/mm^3. In 1975, there were 17 cases of agranulocytosis in Finland, and widespread use of the medication for the treatment of schizophrenia was temporarily halted (Amsler *et al.* 1977; de la Chapelle *et al.* 1977).

Agranulocytosis is a potentially lethal side effect that occurs in less than 1% of patients treated with clozapine in the United States (Alvir *et al.*

1993); therefore, all patients who are taking clozapine are entered into a national registry known as the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program (www.clozapinerems.com). Through this national registry, patients are prescribed the medication only if their ANC count shows no signs of clinically meaningful suppression (Honigfeld 1996). The morbidity and mortality of clozapine-treated patients over a 5-year period was reviewed in 99,502 patients registered through the previous Clozaril National Registry (Honigfeld *et al.* 1998). Among these patients, 2,931 (2.95%) developed leukopenia (WBC count < 3,500/mm^3), and 382 (0.38%) developed agranulocytosis (ANC < 500/mm^3). Twelve of the cases of agranulocytosis (0.012%) were fatal.

When clozapine treatment is discontinued on identification of marked leukopenia, patients usually recover within 14-24 days and without any long-term consequences. However, rechallenging patients who have experienced agranulocytosis almost always leads to recurrence of the problem. The onset of the second episode is more aggressive than that of the first. In nine patients who were known to be rechallenged, the average time to onset of the second episode was 10 weeks shorter (14 weeks) than for the first episode (24 weeks) (Safferman *et al.* 1992). Agranulocytosis has been successfully treated by discontinuing the medication, providing supportive measures, and administering granulocyte colony-stimulating factor, a medication commonly prescribed to patients with medical illnesses that precipitate WBC count suppression (Raison *et al.* 1994; Weide *et al.* 1992; Wickramanayake *et al.* 1995).

In January 2006, Novartis and the FDA issued a notification to clinicians about modifications to the recommended monitoring schedule for patients receiving clozapine (Novartis Pharmaceuticals 2010). This document continues to be useful; however, in October 2015, the guidelines were updated under a unifying national registry, the Clozapine REMS Program (U.S. Food and Drug Administration 2015). In order to prescribe

clozapine, the prescribing physician, dispensing pharmacy, and patient must be registered with the REMS Program. Under the new monitoring guidelines, a patient beginning clozapine treatment must have a baseline

ANC count of no less than 1,500/mm^3 (1,000/mm^3 if the patient has benign ethnic neutropenia). If, during clozapine treatment, a patient's ANC drops below 1,000/mm^3, clozapine must be interrupted; for patients with benign ethnic neutropenia, treatment must be interrupted if their ANC drops below 500/mm^3. Weekly ANC levels must be obtained for 6 months, at which time the frequency can be reduced to every 2 weeks provided that treatment and monitoring have not been interrupted and that WBC counts and ANCs have remained within acceptable ranges. After 1 year, monitoring can be reduced to monthly blood tests.

Cardiac Effects

Clozapine, like other antipsychotic drugs, carries an FDA black box warning against use in elderly patients with dementia-related psychosis, because of an increased risk of death due primarily to cardiovascular and infectious causes (HLS Therapeutics 2023).

Well-known side effects of clozapine on the cardiovascular system include tachycardia, bradycardia, syncope, and orthostatic hypotension. Tachycardia is thought to be attributable to the anticholinergic activity of the medication at the M_2 receptor, leading to vagal nerve inhibition; hypotension is due to a-adrenergic blockade; and bradycardia is thought to be neurally mediated reflex bradycardia, also known as the vasovagal response.

The most worrisome forms of cardiovascular toxicity, however, are clozapine-associated myocarditis and cardiomyopathy. A 2020 meta-analysis that included more than 250,000 patients found that myocarditis occurred in approximately 7 of 1,000 people treated with clozapine and had an absolute death rate of 4 in 10,000 people (Siskind *et al.* 2020). Cardiomyopathy occurred in 6 of 1,000 people, with a death rate of 3 in 10,000.

The detection of cardiac toxicity is challenging because its manifestations (i.e., tachycardia, fatigue, and orthostatic hypotension) are frequently observed in patients treated with clozapine, particularly when the dosage is altered (Lieberman and Safferman 1992). The poor specificity of signs for cardiac toxicity demands that patients with any personal or family history of heart disease be identified, and the threshold for medical evaluation of patients developing respiratory and cardiovascular symptoms must be low (Wooltorton 2002). Therefore, we recommend monitoring patients' C-reactive protein, eosinophil count, and troponins on a weekly basis for the first 4 weeks of therapy. Etiology of the myocarditis and cardiomyopathy remains unclear.

To monitor for hypotension caused by clozapine, we also recommend a slow upward titration of the medication and monitoring of orthostatic vital signs during the first weeks of therapy. Patients should be educated about the risk of orthostatic hypotension and taught to rise slowly from supine positions. Concomitant treatment with b-blocking agents may be necessary for persistent tachycardia. However, b-blockers may exacerbate the hypotensive effects of clozapine and should be used cautiously.

Metabolic Effects

Weight Gain

Weight gain has been observed in both premarketing and postmarketing trials of clozapine (Henderson 2001; Simpson and Varga 1974; Wirshing *et al.* 1998, 1999). Allison *et al.* (1999) performed a meta-analysis of the weight-gain data in short-term trials of medications. The average weight gain observed with clozapine was 4.45 kg, which exceeded the weight gain observed with all other medications in the study, including the conventional agent thioridazine (3.19 kg), a medication known for its weight-gain liability. The weight gain observed with clozapine seems to occur for a prolonged period--up to 40 weeks. In one naturalistic study, Henderson (2001) observed patients in a clozapine clinic for 5 years and noted weight gain occurring for up to 46 months in some patients.

Phase II of the CATIE provided an opportunity to compare weight gain among patients assigned to clozapine, olanzapine, risperidone, and quetiapine (McEvoy *et al.* 2006). The numbers of patients assessed in the analyses were small, with only 45 patients in the clozapine group, 17 in the olanzapine group, 14 in the quetiapine group, and 14 in the risperidone group. Although the differences in weight gain among these agents were not statistically significant, they were interesting, with patients taking clozapine gaining a mean of 0.5 lb/month, compared with 1.0 lb for olanzapine, 0.4 lb for quetiapine, and 0.5 lb for risperidone.

Diabetes

The weight gain observed with clozapine can place patients at risk for significant health problems. Diabetes is naturally the most concerning potential sequela of this weight gain. Numerous case reports have linked clozapine with new-onset diabetes (Wirshing *et al.* 1998). In Henderson's (2001) naturalistic study of 81 clozapine-treated patients observed over a 5-year period, 36.6% of patients developed diabetes.

Patients treated with clozapine should be routinely screened for diabetes and other metabolic abnormalities, including elevated lipid levels. Patients with risk factors for diabetes should be monitored more closely. Reports and clinical experience suggest that in a case of antipsychotic-associated diabetes or diabetic ketoacidosis, discontinuing the antipsychotic agent may lead to reversal of the hyperglycemia and diabetes. During clozapine therapy, we recommend monitoring fasting glucose, cholesterol, and lipid levels at baseline and every 6 months thereafter.

Prevention of weight gain with clozapine, through nutrition and diet counseling, is recommended. Caloric restriction and exercise for 30 minutes/day should be recommended. Screening questions by physicians that we find useful include the following: "Have you noticed if your belt or pants size has changed?" "Have you noticed an increase in thirst or urinary frequency?"

Dyslipidemias

Clozapine treatment is associated with dyslipidemias, including elevations in triglycerides and cholesterol, particularly low-density lipoprotein cholesterol (McEvoy *et al.* 2006; Wirshing *et al.* 2002a).

In 2004, in response to growing concern that most antipsychotic medications may be associated with weight gain and other metabolic changes, the American Diabetes Association and other groups published a set of guidelines for monitoring weight, glucose, and lipids (American Diabetes Association *et al.* 2004). A very comprehensive literature review was conducted by Marder *et al.* (2004) to guide clinicians in monitoring weight, glucose, lipids, and other parameters of physical health in patients with schizophrenia. Labels were changed for all antipsychotic medications, including clozapine, regarding these metabolic risk factors.

Seizures

A well-known side effect of clozapine treatment is the risk for seizures, which are thought to occur in 5%-10% of patients treated with this medication (Welch *et al.* 1994). The cause of seizures is unclear, but rapid escalations in dosage and possibly high plasma levels of clozapine may account for their development (Klimke and Klieser 1995). Clozapine-associated seizures occur most often at dosages greater than 600 mg/day. The relationship between clozapine plasma levels and seizures is somewhat inconsistent in the literature (Simpson and Cooper 1978; Vailleau *et al.* 1996).

The anticonvulsant agents sodium valproate, gabapentin, and topiramate have been used successfully to treat clozapine-induced seizures (Navarro *et al.* 2001; Toth and Frankenburg 1994; Usiskin *et al.* 2000). Topiramate has an advantage over sodium valproate because it is associated with very little weight gain. In cases in our clinic in which patients develop seizures while taking clozapine, we institute rapid loading with anticonvulsant medication and temporarily discontinue the clozapine treatment. We then slowly reintroduce and re-titrate the clozapine once the patient is taking an adequate dose of anticonvulsant medication.

Anticholinergic Effects

Anticholinergic side effects resulting from clozapine's muscarinic receptor antagonism include sedation, weight gain, dry mouth, constipation, and, in some cases, ileus or bowel obstruction. Constipation can be a difficult but important side effect to manage in severely mentally ill individuals, who may not complain about the problem until a medical emergency, such as acute bowel obstruction, occurs. In institutional settings and in prisons, where patients may have little access to exercise and where their fluid intake levels are not monitored, constipation from clozapine can be serious or even fatal (Drew and Herdson 1997; Hayes and Gibler 1995; Levin *et al.* 2002). Typically, constipation can be avoided with proactive modifications to patients' diets and education about adequate fluid intake and exercise. Our preferred medical treatment is prophylactic therapy with sorbitol. We are less inclined to recommend treatments involving bulking agents, particularly in the setting of poor fluid intake. High-fiber diets can also be beneficial.

Other Side Effects

Sedation is one of the most difficult and common side effects of clozapine to manage. Patients often do not want their dosages increased in the setting of increased sedation and will complain of sedation as one of the most annoying consequences of clozapine treatment (Angermeyer *et al.* 2001). In our experience, sedation is usually the limiting factor controlling both the rate at which the dosage of clozapine can be increased and the maximum dosage the patient can tolerate. However, no rigorous studies have been published.

There have been several reports of respiratory arrest or depression during the early stages of treatment with clozapine (HLS Therapeutics 2023). Two of the patients who experienced respiratory arrest were concomitantly taking benzodiazepines.

Sialorrhea is a commonly reported side effect of clozapine (occurring in more than 50% of patients) that can be problematic for patients. Its etiology is unclear, but it does not seem to be caused by the dopamine blockade. It may be mediated through a-adrenergic receptor blockade. Case series and small pilot studies indicate that treating sialorrhea with antiadrenergic agents, such as the clonidine patch; anticholinergic agents, such as benztropine and intranasal ipratropium bromide; or atropine ophthalmic drops administered sublingually may be successful (Calderon *et al.* 2000). We generally recommend that patients sleep with a towel on their pillow because this side effect seems to be most bothersome during the night. Unfortunately, the use of concomitant antiadrenergic or anticholinergic agents adds to the potential side effect burdens of hypotension and constipation, respectively.

Neuroleptic malignant syndrome, a syndrome of unknown etiology that includes hyperthermia, autonomic instability, and severe rigidity, has been reported in several patients treated with clozapine (Anderson and Powers 1991). The etiology of neuroleptic malignant syndrome occurring in the context of clozapine use, as well as that occurring with conventional antipsychotic use, remains unclear.

Hepatotoxicity has been reported with clozapine, especially in the setting of polypharmacy (Macfarlane *et al.* 1997; Wirshing *et al.* 1997). Asymptomatic elevation of transaminase levels was observed most often, affecting between 30% and 50% of patients treated with clozapine. Icteric hepatitis was uncommonly seen in Macfarlane et al.'s (1997) review of clozapine-related hepatotoxicity and noted in 84 of 136,000 patients (0.06%). Fatal acute fulminant hepatitis has been documented in 2 patients (0.001%). Although serious toxicity is rare, prescribers of clozapine should be aware of its hepatotoxic potential.

Sexual side effects, including priapism and impotence, have been reported with clozapine. Urinary retention and bladder dysfunction can also result from clozapine. In a study that surveyed patients' sexual side effects, we found that patients taking clozapine actually had fewer sexual complaints than those taking other antipsychotic medications (fluphenazine and risperidone) (Wirshing *et al.* 2002b).

Dizziness, vertigo, and headache have also been reported with clozapine (HLS Therapeutics 2023).

Clozapine has been shown to induce de novo obsessive-compulsive symptoms (OCS). In a naturalistic study following 543 patients, 38.9% of those taking clozapine reported OCS, compared with 20.1% of those taking olanzapine and 23.2% of those taking risperidone (Scheltema Beduin *et al.* 2012). Two case studies of patients with bipolar disorder taking clozapine reported a clear temporal relationship between initiation of clozapine and OCS (Lemke and Bustillo 2013). The severity of OCS appears to be dosage related, which suggests that clozapine dosage reduction may be effective

(Kim *et al.* 2020). There is support for treating these symptoms with selective serotonin reuptake inhibitors, clomipramine, and aripiprazole. In our experience, patients with OCS often benefit from combining medications with cognitive-behavioral therapy for OCD.

Although this daunting array of side effects--along with the management of the risk of agranulocytosis--makes the treatment of patients with clozapine complex, it is common for patients to report a sense of relief from the dysphoric moods they experienced with conventional drugs. Additionally, the freedom from EPS may account for the enhanced sense of well-being in patients treated with clozapine.

Discontinuation and Reinitiation (Rechallenge)

In their 2013 review, Nielsen *et al.* (2013) posited that clozapine should be discontinued in all cases of agranulocytosis (ANC < 500/mm^3), myocarditis, and cardiomyopathy

but should not be discontinued for known benign side effects such as eosinophilia, benign neutrophilia or leukocytosis, idiopathic sinus tachycardia, or benign hyperthermia. Seizures should not be an absolute contraindication to clozapine treatment because they may be managed with initiation of an anticonvulsant, either to prevent or to stabilize seizures prior to initiation of clozapine.

Historically, if a patient's WBC decreased below 2,000/mm^3 or their ANC decreased below 1,000/mm^3, clozapine was discontinued and the patient was regarded as non-rechallengeable--that is, re-initiation of clozapine should not be attempted. With new FDA regulations implemented in October 2015, clinicians were given the freedom to evaluate each patient on a case-by-case basis and to weigh the relative risk of psychosis with risk of agranulocytosis. If and when a clinician opts to restart clozapine in a patient, regardless of the circumstance, they must begin at 12.5 mg orally once or twice daily and titrate upward gradually. If the patient has not experienced adverse effects from clozapine in the past, the re-initiation dosage may be titrated upward more rapidly than their initial titration.

Drug-Drug Interactions

As previously mentioned, clozapine is predominantly metabolized by CYP1A2, although CYP2D6 and CYP3A3/4 also contribute to its metabolism (Buur-Rasmussen and Brosen 1999). Smoking, which induces CYP1A2, lowers clozapine plasma levels, and dosages of clozapine up to twice the normal dosage may be required to maintain a therapeutic serum level. Use of phenytoin and rifampin may also decrease clozapine plasma concentrations (HLS Therapeutics 2023). Fluvoxamine and ciprofloxacin, potent inhibitors of CYP1A2, dramatically increase plasma levels of clozapine (Heeringa *et al.* 1999; U.S. Food and Drug Administration 2023), and on occasion, adverse effects are seen (Koponen *et al.* 1996). Other reports suggest that inhibitors of CYP2D6, including paroxetine and fluoxetine, can elevate clozapine levels (Joos *et al.* 1997; Spina *et al.* 1998). In general, if the patient initiates a strong CYP1A2 inhibitor, use one-third of their normal clozapine dosage. For those initiating moderate or weak CYP1A2 inhibitors or CYP2D6 or CYP3A3/4 inhibitors, consider decreasing their clozapine dosage. If they initiate strong CYP3A3/4 inducers or moderate or weak CYP1A2 inducers, monitor for decreased effectiveness and consider increasing their clozapine dosage if necessary (HLS Therapeutics 2023). CYP-related problems can be avoided by monitoring clozapine plasma levels while gradually increasing clozapine from a low starting dosage. Clozapine should not be used together with other drug products known to have the potential to suppress bone marrow function. Clozapine may potentiate the hypotensive effects of antihypertensive and anticholinergic drugs (HLS Therapeutics 2023).

Conclusion

Clozapine maintains an important place in the treatment of severe psychosis. Side effects, including agranulocytosis, cardiomyopathy, seizures, sedation, and weight gain, make it the most difficult antipsychotic to prescribe. For this reason, clozapine should be reserved for patients who have failed to respond to one or more other antipsychotics. On the whole, however, this very effective treatment is underutilized in most communities, which is unfortunate because a patient's illness should never be deemed "treatment refractory" or the patient labeled a "partial responder" until the individual has received an adequate trial of clozapine.

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CHAPTER 27

Olanzapine

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History and Discovery

The story of specific antipsychotic medications for patients with schizophrenia and other severe psychiatric illnesses began in the early 1950s, when chlorpromazine was first given to psychotic patients in France (Delay and Bernitzer 1952). The antipsychotic qualities of this compound, as well as its "tranquilizing" effect, were dramatic and substantial. Studies performed around the world during the 1950s showed the usefulness of this new compound and of the others that followed. Multicenter trials of antipsychotic medications found that the approved medications were substantially and significantly better than placebo (Guttmacher 1964), and, despite the range of chemical structures, their clinical effects were similar. In addition, the need to investigate these new medications for psychiatric illness led to improved clinical trial methodology for the field. During the 1960s, randomized and placebo-controlled trials became the standard for assessing the new medications for schizophrenia and led to the adoption of antipsychotic medications as the standard somatic treatment for this condition.

Over time, however, the adverse effects of these medications began to be recognized as more troublesome. For example, many patients complained of medication-induced parkinsonism, dystonias, slowed thinking, blunted affect, akathisia, and tardive dyskinesia. These side effects were uncomfortable for patients taking the medications and, in many cases, led to poor treatment adherence. Seeking ways to achieve the same treatment benefits with fewer side effects, investigators at Eli Lilly began to screen numerous compounds for potentially useful psychotropic properties. In 1990, the company applied for and received a patent for the compound olanzapine. This compound had many structural similarities to clozapine, which in 1989 had been approved for use in treating refractory schizophrenia. Hailed as a novel second-generation antipsychotic (SGA) drug, clozapine was thought to have potential for schizophrenia, mania, and anxiety and was noted for both its efficacy and its lack of neurological side effects.

Olanzapine was first given to patients with schizophrenia in 1995 (Baldwin and Montgomery 1995). The patients in that study experienced a substantial decrease in their symptoms while receiving 5-30 mg/day of the compound. The researchers noted a low degree of extrapyramidal side effects (EPS), although they became concerned regarding the elevation of liver enzymes, for which one patient had to discontinue the study. Despite this, the initial testing of olanzapine had useful results and led to a program of three pivotal trials of the drug. These first three controlled studies compared olanzapine (at two fixed dosages, 1 mg/day and 10 mg/day) against placebo (Beasley *et al.* 1996a); olanzapine at three fixed dosages (low, medium, or high) against olanzapine at 1.0 mg/day or haloperidol at 15 mg/day or placebo (Beasley *et al.* 1996b); and olanzapine against haloperidol in a large international study (Tollefson *et al.* 1997). The positive results for olanzapine led to FDA approval in 1997 and to subsequent widespread use in the United States and around the world.

Structure-Activity Relations

Olanzapine is a thiobenzodiazepine derivative that bears a close structural resemblance to clozapine. Its formal chemical name is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine. Structurally, olanzapine differs from clozapine by two additional methyl groups and the lack of a chloride moiety (Figure 27-1). The in vitro receptor binding profiles of olanzapine and clozapine are relatively similar; according to the package insert, olanzapine is known to have a high affinity for dopaminergic ($D_{1\text{-}4}$), serotonergic (5-$HT_{2A/2C}$, 5-HT_6), histaminergic (H_1), and a-adrenergic (a_1) receptors, with moderate affinity for muscarinic ($M_{1\text{-}5}$) receptors and weak activity at benzodiazepine, g-aminobutyric acid A ($GABA_A$), and b-adrenergic receptors (Eli Lilly 2021).

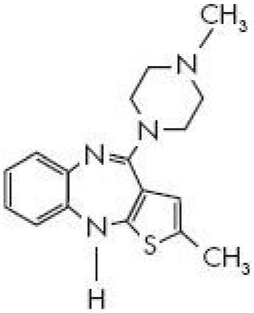

FIGURE 27-1. Chemical structure of olanzapine.

Pharmacological Profile

In vitro and preclinical behavioral studies of olanzapine predicted significant antipsychotic activity with a low propensity to induce EPS. Because clozapine is the prototype for SGA action, it serves as the yardstick for "atypicality" of comparator compounds. Despite widespread general use of the term *atypical* to refer to any antipsychotic developed after clozapine, the term was originally coined to connote medications with an EPS risk no greater than that of placebo. Although olanzapine does carry a lower risk of tardive dyskinesia than do many other antipsychotics, its risk is still appreciably greater than that of placebo, and therefore the term *atypical* has fallen out of fashion (Farah 2013).

One property that may lower a compound's risk of EPS is nonselective binding of dopamine receptors. Classical antipsychotics selectively block dopamine D_2-like (D_2, D_3, and D_4) receptors over D_1-like (D_1 and D_5) receptors--for example, haloperidol has a D_2:D_1 binding ratio of 25:1. Clozapine nonselectively binds all five dopamine

receptor subtypes, with a D_2:D_1 ratio of 0.7:1, whereas olanzapine is only partially selective for the D_2-like group, with a D_2:D_1 ratio of approximately 3:1, intermediate between those of haloperidol and clozapine.

In animal models predictive of antipsychotic efficacy, olanzapine produces effects indicating dopamine antagonism, with a low propensity to produce EPS. For example, in rats, olanzapine reduces climbing behavior induced by apomorphine and antagonizes stimulant-induced hyperactivity, both characteristic of antipsychotic effects. The ratio of the dosage needed to produce catalepsy to the dosage needed to inhibit conditioned avoidance is higher for olanzapine than for conventional agents (Moore 1999).

An additional mechanism whereby dopamine antagonists may exert antipsychotic effects with minimal EPS is through selective activity in the A10 dopaminergic tracts from the ventral tegmentum to mesolimbic areas compared with effects antagonizing the A9 nigrostriatal projections that mediate EPS. Olanzapine in chronic administration, like clozapine, selectively inhibits firing of A10 neurons without significant inhibition of A9 tracts (Stockton and Rasmussen 1996a). Olanzapine shows increased c-Fos activity in the nucleus accumbens relative to the dorsolateral striatum, thus demonstrating selective blockade of the mesolimbic dopamine tract compared with the nigrostriatal tract (Robertson and Fibiger 1996).

Another theory regarding olanzapine's efficacy considers its fleeting effects at the D_2 receptor, coupled with the regional selectivity of these compounds (Seeman 2002). Olanzapine's D_2 receptor occupancy saturation--which has been shown to be intermediate between that of clozapine and that of haloperidol--may be responsible for its decreased risk of EPS (Tauscher *et al.* 1999).

Amphetamine administration in rats is often used as a model for psychosis. The sympathomimetic activity and dopamine release provide a target for testing antipsychotic medications. Olanzapine disrupts the activity of amphetamines in rats (Gosselin *et al.* 1996). It was shown in a rat model to decrease dopamine release in the A10 dopaminergic neurons of the ventral tegmentum to a greater extent than in the A9 dopaminergic neurons of the striatum after chronic administration and after an amphetamine challenge (Stockton and Rasmussen 1996a, 1996b). Another model of psychosis in rats is produced by administration of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine. Chronic phencyclidine use in humans is associated with symptoms similar to those in schizophrenia, including negative symptoms, thus making it a putative model for schizophrenia (Krystal *et al.* 1994). Olanzapine has been shown to decrease the hyperactivity of NMDA receptors under chronic phencyclidine administration, which may have a bearing on its effect on negative symptoms (Ninan *et al.* 2003). With chronic administration, glutamatergic activity continues to be affected by olanzapine (Jardemark *et al.* 2000). Despite these findings, olanzapine has no direct affinity for the NMDA receptor (Stephenson and Pilowsky 1999).

Receptor-binding studies show that olanzapine has a broad range of neurotransmitter effects (Bymaster *et al.* 1996). Although it has potent muscarinic M_{1-5} receptor affinity in vitro (another contributor to putative anti-EPS effects), in practice few patients treated with olanzapine experience clinically significant anticholinergic side effects. a_1-Adrenergic and H_1 histaminergic antagonism contributes to olanzapine's adverse-effect profile of orthostatic hypotension (a_1), sedation (H_1), and possibly weight gain (H_1). Olanzapine, like other SGAs, has a higher affinity for 5-HT_2 receptors than for D_2 receptors (Kapur *et al.* 1999). There is also indirect evidence that olanzapine blocks 5-HT_{2C} receptors (Sharpley *et al.* 2000). Olanzapine has little or no effect on a_2- and b-adrenergic, H_2, nicotinic, GABA, opioid, sigma, or benzodiazepine receptors.

Pharmacokinetics and Disposition

Olanzapine is well absorbed after oral administration, with peak concentrations typically occurring 4-6 hours after ingestion. Approximately 40% of a given dose undergoes first-pass metabolism and therefore does not reach the systemic circulation, and food has little effect on olanzapine's bioavailability (Eli Lilly 2021).

Two bioequivalent oral formulations of olanzapine are currently available: a standard oral tablet and an oral disintegrating tablet. Oral disintegrating tablets dissolve rapidly in saliva in the mouth and are then swallowed, and absorption of olanzapine occurs through the gut. Oral disintegrating tablets are favored by some because they allow the clinician to verify that the medication was taken. Markowitz *et al.* (2006) noted that although oral disintegrating tablets are absorbed slightly more rapidly than the standard oral tablets, the onset of effect is approximately the same, regardless of whether an orally disintegrating tablet or a standard oral tablet is administered. After a 12.5-mg oral dose of ^{14}C-labeled olanzapine, approximately 57% of the radiocarbon is recovered in urine and 30% in feces. In vitro studies suggest that olanzapine is approximately 93% protein bound, binding primarily to albumin and a_1-acid glycoprotein (Kassahun *et al.* 1997).

Olanzapine is available as an intramuscular preparation, intended for treatment of the acute agitation typically seen in schizophrenia or in acute manic episodes of bipolar disorder. The peak plasma concentration is typically reached between 15 and 45 minutes after administration. The potency of intramuscular olanzapine is nearly five times greater than that of the orally administered drug, based on plasma levels. Clinical antipsychotic effect onset with intramuscular olanzapine is evident within 2 hours of administration, with benefits lasting for at least 24 hours (Kapur *et al.* 2005).

Olanzapine is also available in a long-acting injectable (LAI) preparation composed of a dihydrate form of olanzapine pamoate (Eli Lilly 2014). As a dihydrate molecule, it is less soluble in water than a monohydrate and thus has the longer half-life required for a depot formulation. This formulation is designed to be administered once every 4 weeks. As the pamoate moiety converts to olanzapine rapidly in the bloodstream, extreme caution must be used to inject directly into a muscle, and patients must be observed for 3 hours after injection to monitor for delirium or sedation that could result from accidental injection into vasculature (Eli Lilly 2021).

Finally, olanzapine is available in two different combined preparations. The olanzapine/fluoxetine combination (OFC) tablet provides fixed doses of olanzapine and fluoxetine for treatment of bipolar depression (Eli Lilly 2009). Overall, few pharmacokinetic changes result from adding fluoxetine to olanzapine, and those that do occur are generally related to cytochrome P450 (CYP) 2D6 inhibition. There is no change in the overall half-life of olanzapine. Although minor yet statistically significant changes occur in the concentration of olanzapine when it is coadministered with fluoxetine, these changes are not *clinically* significant and do not alter the side-effect profile of olanzapine (Gossen *et al.* 2002). Olanzapine is also available in a combination with samidorphan (Alkermes 2021), an opiate antagonist that is FDA approved for use in the same conditions as olanzapine. The addition of samidorphan has been shown to help decrease the risk of weight gain compared with olanzapine alone, with no changes in pharmacokinetics of the olanzapine (Martin *et al.* 2019).

Olanzapine is extensively metabolized to multiple metabolites, but primarily to 10-*N*-glucuronide and 4'-*N*-desmethylolanzapine (Macias *et al.* 1998). In vitro studies examining the oxidative metabolism of olanzapine suggest that CYP1A2 is the enzyme primarily responsible for the formation of 4'-*N*-desmethylolanzapine, flavin-containing monooxygenase-3 (FMO3) is responsible for the formation of 4'-*N*-oxide olanzapine, and CYP2D6 is the primary enzyme responsible for the formation of 2-hydroxymethyl olanzapine (Ring *et al.* 1996b). Although CYP1A2 appears to be a major route of metabolism, olanzapine clearance in one study was not significantly correlated with the salivary paraxanthine-to-caffeine ratio (thought to be a measure of CYP1A2 activity) (Hagg *et al.* 2001). Another analysis, however, found that the 4'-*N*-desmethylolanzapine-to-olanzapine plasma metabolic ratio significantly correlated with olanzapine clearance (Callaghan *et al.* 1999). Olanzapine pharmacokinetic parameters do not differ significantly between extensive and poor metabolizers of CYP2D6 (see Hagg *et al.* 2001).

Olanzapine shows linear pharmacokinetics within the recommended dosage range (Callaghan *et al.* 1999). Mean half-life is 36 hours, mean clearance is 29.4 L/hour, mean volume of distribution is 19.2 L/kg, and area under the concentration-time curve over 24 hours ($AUC_{0\text{-}24}$) is 333 ng*hour/mL. The half-lives of the two major metabolites (4'-*N*-desmethylolanzapine and 10-*N*-glucuronide) are 92.6 and 39.6 hours, respectively (Macias *et al.* 1998). Other analyses also have found the mean half-life of olanzapine to be approximately 30 hours and the mean apparent clearance to be approximately 25 L/hour (Callaghan *et al.* 1999; Eli Lilly 2021; Kassahun *et al.* 1997). Once-daily administration of olanzapine produces steady-state concentrations in about 1 week that are approximately twofold higher than concentrations after a single dose (Callaghan *et al.* 1999).

Clearance of olanzapine is approximately 25%-30% lower in females than in males, based on results of population pharmacokinetic analyses (Callaghan *et al.* 1999; Patel *et al.* 1996). A study of 20 male and 7 female patients with schizophrenia receiving olanzapine also found that females had higher trough concentrations after receiving 1 week of olanzapine 12.5 mg/day (Kelly *et al.* 1999). Despite the differences in clearance and plasma levels, there is no difference between sexes in the incidence of EPS or other movement disorders (Aichhorn *et al.* 2006).

Olanzapine's pharmacokinetics in elderly persons and in children differ from those in other adults. In elderly individuals, olanzapine clearance is approximately 30% lower than in younger individuals, and the half-life is approximately 50% longer (Callaghan *et al.* 1999; Patel *et al.* 1996). A study of eight children and adolescents (ages 10-18 years) found pharmacokinetic parameters similar to those reported in nonsmoking adults, with an average T_{max} (time required to reach the maximal plasma concentration) of 4.7 hours, an average apparent oral clearance of 9.6 L/hour, and an average half-life of 37.2 hours (Grothe *et al.* 2000). The highest concentrations were seen when smaller-sized patients received dosages greater than 10 mg/day; therefore, dosing should take into consideration the size of the child.

Impairment in either hepatic or renal function has not been associated with altered olanzapine disposition. In a study of four healthy individuals and eight patients with hepatic cirrhosis, no significant differences in olanzapine pharmacokinetics were found, although urinary concentrations of olanzapine 10-*N*-glucuronide were increased in patients with cirrhosis. A study comparing olanzapine pharmacokinetics in six subjects with normal renal function, six subjects with renal failure who received an olanzapine dose 1 hour before hemodialysis, and six subjects with renal failure who received an olanzapine dose during their 48-hour interdialytic interval did not find any significant differences. These data suggest that olanzapine dosage does not need to be adjusted in patients with renal or hepatic disease (Callaghan *et al.* 1999).

Mechanism of Action

Regarding olanzapine's mechanism of action in the treatment of schizophrenia, it should be noted that no established molecular mechanism can unify the symptoms of schizophrenia. No precise animal or in vitro model for the illness exists, nor is there a consensus on its precise etiology or pathophysiology. Numerous neurochemical hypotheses have been proposed, including theories implicating abnormalities in dopaminergic, glutamatergic, serotonergic, and other systems, such as neurotensin (Boules *et al.* 2007) or neuregulin (Benzel *et al.* 2007). However, the discovery that multiple receptor types exist for each neurotransmitter has added many layers of complexity to the search for explanations regarding the root causes of schizophrenia. Thus, it is no longer possible to use broad terms such as "increased dopamine" when discussing ideas about the etiology of the disorder.

Despite these caveats regarding our rudimentary knowledge of the nature of schizophrenia, it is important to note that all approved antipsychotic medications have a significant effect on the dopaminergic system, largely through the blockade of D_2 receptors (Kapur and

Remington 2001). Even though there are substantial differences in D_2 receptor affinity among the traditional antipsychotics and the SGAs, they all are either full antagonists or partial agonists at the D_2 receptor. Of interest is evolving research indicating the importance of multiple-receptor blockade to the effectiveness of the SGA class. As the various neurotransmitter systems have been investigated in relation to the neuropsychopharmacology of schizophrenia, evidence is emerging that the SGAs, and olanzapine in particular, may improve different schizophrenia symptom domains through effects on 5-HT receptors, on multiple-receptor binding, on region-specific and more fleeting binding to dopamine receptors, on glutamate neurotransmission, and perhaps on neuropeptide neurotransmitters. In the following paragraphs, we discuss each of these specific ideas about olanzapine's mechanism of action in turn.

In clinical investigations with PET imaging, Kapur *et al.* (1998) showed that olanzapine at a wide range of dosages blocks a high percentage ([?] 95%) of 5-HT_{2A} receptors and blocks dopamine receptors in a dose-dependent fashion--crossing the putative antipsychotic blockade line at dosages commonly used to diminish psychotic symptoms of schizophrenia. This study indicated that olanzapine's primary mechanism was related to the blockade of dopamine receptors and additionally noted that olanzapine showed stronger affinity for 5-HT_{2A} receptors than for dopamine receptors at all dosage ranges.

A more compelling hypothesis regarding the mechanism of olanzapine's effects emerged from in vivo PET scanning work performed in a series of experiments at the University of Toronto and in Sweden. Results of the initial PET scanning studies of patients receiving clozapine indicated that atypical D_2 receptor binding was occurring (Farde and Nordstrom 1992; Farde *et al.* 1992; Kapur *et al.* 2000). The group subsequently found similar unusual D_2 receptor binding with quetiapine and, to some degree, olanzapine (Kapur *et al.* 1998). The authors proposed that the so-called atypical antipsychotic effect--successful treatment of psychotic symptoms with limited induction of movement disorder side effects--may be the result of a "fast-off" property of some SGAs, wherein the drug blocks the D_2 receptor but leaves it quickly, a receptor occupancy pattern that effectively decreases psychosis yet causes minimal interference to the body's own dopamine receptor activity. Thus, for olanzapine, this mechanism might help explain how the drug can exert strong therapeutic effects on schizophrenia symptoms yet cause few EPS at standard dosages. From a clinical viewpoint, it is important to note that at higher olanzapine dosages (30 mg/day), greater dopamine receptor blockade is seen, and movement disorder side effects such as akathisia are more likely to occur.

For more than 40 years, there has been substantial interest in the role of glutamate, an excitatory neurotransmitter, in the pathophysiology of schizophrenia (e.g., Moghaddam and Javitt 2012). Its inclusion in theories about the development of schizophrenia is supported by the psychotomimetic properties of glutamate antagonists such as phencyclidine and ketamine. These NMDA receptor antagonists induce a group of behaviors that often show closer parallels to schizophrenia than do those induced by dopamine sympathomimetic agents, in both mice and humans. Clinical trial evidence points to the potential usefulness of glutamatergic agonists (e.g., D-cycloserine) in treating schizophrenia (Kantrowitz *et al.* 2010). One way of examining the potential effectiveness of medication is to look at changes in deficits in *prepulse inhibition* (i.e., attenuation of the startle response), a measure of sensory motor gating that is diminished in patients with schizophrenia and can be similarly diminished pharmacologically through administration of phencyclidine (Dulawa and Geyer 1996). In a study of rats with isolation-induced disruption of prepulse inhibition, both quetiapine and olanzapine successfully reversed the prepulse inhibition deficit (Bakshi *et al.* 1998).

In summary, olanzapine works at least at the dopamine, 5-HT, and glutamate receptors. Current theories suggest that dopamine receptor-blocking capabilities are a necessary but not sufficient requirement for antipsychotic effectiveness. The other studied mechanisms, when taken in total, may be the factors leading to olanzapine's broad efficacy and side-effect profile.

Indications and Efficacy

Olanzapine initially received FDA approval for the treatment of psychotic disorders. Currently, it has multiple indications, including treatment of schizophrenia; acute treatment of manic or mixed states in bipolar disorder; and maintenance treatment of bipolar disorder, both as monotherapy and as an adjunct to mood stabilizer therapy. The OFC preparation has an FDA indication for bipolar depression and treatment-resistant depression. The olanzapine/samidorphan combination is also indicated for schizophrenia and bipolar I disorder (acute and maintenance treatment) in adults. Intramuscular olanzapine carries an indication for acute agitation in schizophrenia and bipolar mania. Olanzapine is approved for adults and for children ages 13-18 years.

In addition to the approved indications, olanzapine has been studied--and at times used with limited evidence--in several other illnesses. In this section, we present the evidence base supporting the use of olanzapine for its FDA-indicated uses as well as for off-label uses.

Approved Indications

Schizophrenia

As noted earlier, olanzapine was originally developed as a medication with potential for treating schizophrenia, mania, and anxiety. To gain FDA approval for the treatment of schizophrenia, olanzapine was tested in four pivotal studies to assess the compound for efficacy, safety, and dosage range. The earliest testing was an assessment of dosages of 5-30 mg/day following an initial starting dosage of 10 mg/day. Brief Psychiatric Rating Scale (BPRS) scores were reduced substantially, and EPS incidence was low (Baldwin and Montgomery 1995). These encouraging results led to further studies and pointed to a dosage range to be tested. Notably, the Schizophrenia Patient Outcomes Research Team study found that olanzapine was associated with significant metabolic risks and suggested that it should not be considered a first-line treatment for individuals experiencing their first episode of schizophrenia (Buchanan *et al.* 2010).

Efficacy studies. The first pivotal study compared two dosages of olanzapine (1 mg/day and 10 mg/day) with placebo in a large international sample. The 10 mg/day dosage was statistically significantly superior to placebo on objective rating scales (Beasley *et al.* 1996a). The second pivotal study was a dose-ranging comparison of olanzapine versus haloperidol and placebo, also in a large international sample. Three dosage ranges for olanzapine were included: 1) low (5 +- 2.5 mg/day), 2) medium (10 +- 2.5 mg/day), and 3) high (15 +- 2.5 mg/day). Haloperidol was dosed to 15 +- 2.5 mg/day. Olanzapine at the medium and high dosage ranges and haloperidol were associated with significant improvements compared with placebo (Beasley *et al.* 1996b). Beasley *et al.* (1997), using the same sample, further demonstrated that acute EPS were reported less frequently in all olanzapine dosage groups than in the haloperidol group. Tollefson and Sanger (1997) reanalyzed data from the first two studies and found that olanzapine had a direct therapeutic effect on negative symptoms that was not mediated by its effects on positive symptoms, EPS, or mood.

Another large international multicenter trial used a flexible dosing strategy to show olanzapine's clinical superiority to haloperidol on positive symptoms, negative symptoms, comorbid depression, EPS, and overall drug safety. In this study, patients were started on olanzapine or haloperidol at dosages ranging from 5 to 20 mg/day. Ultimately, patients received olanzapine 13.2 mg/day or haloperidol 11.8 mg/day (Tollefson *et al.* 1997).

The group of studies just described led to olanzapine's approval for psychosis (later changed to schizophrenia). Several other studies have confirmed olanzapine's efficacy in the treatment of schizophrenia. With its added benefit of low movement-disorder side effects, olanzapine has become an important addition to the armamentarium of the psychiatrist treating schizophrenia. Leucht *et al.* (1999) reported that olanzapine was statistically more effective than placebo (moderate effect) and more effective than haloperidol (small effect) on global schizophrenia symptomatology.

A large National Institute of Mental Health-funded investigation sought to compare the SGAs olanzapine, risperidone, quetiapine, and ziprasidone with perphenazine to understand the efficacy and side-effect profiles of newer versus older antipsychotic medications (Lieberman *et al.* 2005). This project, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), was designed to provide a double-blind yet reasonably naturalistic setting for clinicians to treat patients, using time to discontinuation for any reason as the primary outcome variable. Although olanzapine had the longest time to all-cause discontinuation of any medication in the trial, it also had the highest rate of discontinuation due to metabolic complications such as weight gain, whereas perphenazine had the highest rate of discontinuation due to EPS. Overall, however, the discontinuation rate was high for all medications, with nearly 75% of patients changing medications within the 18-month study duration. Much discussion and written commentary has ensued since the initial findings were published, including analyses of cost-effectiveness (Rosenheck *et al.* 2006), of the effects of antipsychotic medication on psychosocial functioning (Swartz *et al.* 2007), and of the impact of switching medications (Essock *et al.* 2006), as well as numerous editorials about the treatment implications of the study.

Schizophrenia is often not fully responsive to antipsychotic treatment. This places olanzapine in a difficult position in treatment algorithms because metabolic side effects limit its use in early psychosis, but its use is not supported in lieu of clozapine in refractory psychosis. Assessment of olanzapine in patients with treatment-refractory illness did not support its usefulness in a stringent nonresponder protocol (Conley *et al.* 1998). A second phase of the CATIE project examined the use of clozapine in patients with treatment-refractory illness and found, based on the time to discontinuation, that clozapine was a superior treatment for patients whose illness had not responded to other SGAs (McEvoy *et al.* 2006).

Although early research noted olanzapine's beneficial effects on negative symptoms and cognitive symptoms of schizophrenia, these effects were not as strong as the drug's effects on positive symptoms. In a flexible-dose comparison between risperidone and olanzapine in patients followed for 1 year, olanzapine-treated patients showed significantly greater improvement on Scale for the Assessment of Negative Symptoms (SANS) scores than did risperidone-treated patients (Alvarez *et al.* 2006). In contrast, a study by researchers from Eli Lilly followed patients taking either quetiapine or olanzapine for 6 months and found similar improvements on the SANS at study completion in both groups (Kinon *et al.* 2006). In a meta-analysis of 50 studies of SGAs (Komossa *et al.* 2010), no difference in short-, medium-, or long-term improvement of negative symptoms (as measured by Positive and Negative Syndrome Scale [PANSS] negative, BPRS negative, and/or SANS total scores) was found between olanzapine and the other medications, which included amisulpride, clozapine (1 of 12 studies found clozapine to be superior as measured by SANS total scores), quetiapine, and ziprasidone (1 of 2 studies found olanzapine to be superior on PANSS negative scores, but overall no difference was found). An additional meta-analysis of 21 randomized controlled trials (RCTs) (*n* = 3,451 subjects) concluded similarly that olanzapine did not show benefit over placebo on negative symptoms (Krause *et al.* 2018).

Cognitive functioning is the most important indicator of schizophrenia prognosis (Green 2006). In a 1-year comparison of olanzapine with risperidone, both groups showed modest benefits on a cognitive function battery (Gurpegui *et al.* 2007). In a study conducted over a 1-year period by Eli Lilly researchers in Spain, olanzapine-treated patients showed greater benefit in social functioning than did risperidone-treated patients, as assessed by scores on the Social Functioning Scale. The greatest difference was in occupation/employment, but improvements were also seen on measures of independence, social engagement, and recreation (Ciudad *et al.* 2006).

In an 8-week double-blind, placebo-controlled study, the LAI formulation of olanzapine showed a statistically significant separation from placebo (as measured by decreases in PANSS total scores) that was evident by day 7 (Lauriello *et al.* 2008). Another study of olanzapine LAI that involved a longer period of treatment--24 weeks--found that a high percentage of subjects remained free of psychotic exacerbation (Kane *et al.* 2010).

Studies have investigated olanzapine's efficacy in the treatment of schizophrenia spectrum and other psychotic disorders in adolescents. An important caveat is that these studies are for those who have experienced psychotic symptoms beyond the threshold for diagnosis. Olanzapine is not indicated for use in those considered at risk for development of psychosis (McGlashan *et al.* 2006). In a systematic review of the literature on antipsychotic use in children, SGAs were shown to be beneficial overall in improving psychotic symptoms (Jensen *et al.* 2007). Olanzapine's safety profile in adolescents is similar to its profile in adults, although its adverse effects on weight and prolactin are more significant in young people (Kryzhanovskaya *et al.* 2009). A double-blind, flexible-dose study demonstrated comparable efficacy for risperidone, olanzapine, and haloperidol in young people with psychosis (Sikich *et al.* 2004). A similar trial of olanzapine, risperidone, and quetiapine in early psychosis found equivalent rates of discontinuation for the three drugs over a 52-week period, with olanzapine and risperidone showing slightly greater reductions on PANSS positive scores compared with quetiapine (McEvoy *et al.* 2007). In late 2009, olanzapine received FDA approval for the treatment of schizophrenia in teenagers, but with the recommendation that clinicians first consider other agents given concerns about metabolic

consequences (for further discussion, see "Side Effects and Toxicology" later in this chapter).

At the other end of the age spectrum, olanzapine has been investigated in the treatment of psychotic disorders in elderly persons. Olanzapine, like all antipsychotic medications, carries an FDA black box warning regarding an increased risk of stroke associated with its use in elderly individuals with dementia-related psychosis. (Use of olanzapine in dementia is discussed in greater detail later in this chapter; see "Dementia-Related Agitation and Psychosis.") A study of olanzapine versus haloperidol in a group of older patients with chronic schizophrenia found a statistical advantage for olanzapine (Krause *et al.* 2018). In a study of olanzapine in 94 acutely ill inpatients age 65 years or older, some with psychosis, Hwang *et al.* (2003) reported mean reductions from baseline of greater than 50% on BPRS scores, thus illustrating olanzapine's usefulness in treating a broad range of psychotic symptoms in older patients. As with any treatment used in elderly persons, special care must be taken to avoid cardiovascular complications as well as risks associated with olanzapine's anticholinergic properties. With olanzapine, orthostatic hypotension, oversedation, and thus the risk of falls must be factored into the dosing decision (Gareri *et al.* 2006).

Treatment approaches. Early studies of olanzapine assessed dosages ranging from 5 to 30 mg/day. When olanzapine was initially released, it was recommended that the medication be started at a dosage of 10 mg/day, often given as a bedtime dose. Although the FDA-approved maximum dosage is 20 mg/day, it is not uncommon for olanzapine to be used off-label at dosages up to 40 mg/day, particularly in acute settings. Looking at the dose-response curves, the ED95, corresponding to the point on the curve that shows a 95% response rate, was 15.1 mg. The dose-response curve had not flattened fully by that dose, however, meaning that higher doses may in fact also be beneficial, particularly in certain individuals (Leucht *et al.* 2020). In the flexible-dosing segment of the CATIE, in which the available dosages were 7.5, 15.0, 22.5, and 30.0 mg/day, the average dosage was 20.1 mg/day (Lieberman *et al.* 2005). Because some patients appear to have an inadequate response to olanzapine at the recommended dosages, clinicians have assessed its usefulness at dosages above the recommended 20 mg/day. Many hospital clinicians employ a loading strategy with olanzapine, particularly in young, otherwise healthy patients presenting with acute agitation, using dosages up to 40 mg/day for the first 2 days and gradually decreasing to a target dosage of 20-30 mg/day (Brooks *et al.* 2008). Although sedation and hypotension must be watched for in any individual patient, increased rates of those side effects were not seen in a study comparing the loading-dose strategy with 10 mg/day dosing (Baker *et al.* 2003). Conversely, patients early in their course of psychosis, particularly if not presenting with acute agitation, may benefit from lower dosages and a more gradual titration if olanzapine is to be used (Keating *et al.* 2021).

Typically, agitated patients are best treated with the rapid-dissolving preparation of olanzapine. The rapid-dissolving tablet formulation is preferable to the conventional pill in the acute setting, particularly when some sedation is also needed, given its faster onset of action and the decreased risk of "cheeking" the medication. When patients are severely agitated, use of injectable olanzapine may also be necessary. The intramuscular preparation has a rapid onset of action similar to that of dissolvable tablets and a certainty of delivery that is imperative in an emergency. It has been

shown to be superior to placebo at dosages of 10 mg/day and as effective as haloperidol, with significantly fewer side effects (Breier *et al.* 2002). Case reports caution against the use of olanzapine in conjunction with intramuscular lorazepam because of the risk of hypotension, although recent research has called that warning into question (Williams 2018).

For patients who require long-term treatment, LAI olanzapine can be used on a biweekly or once-monthly administration schedule. Because of concerns regarding cases of delirium and even coma reported in early studies, individuals receiving LAI olanzapine must be observed for 3 hours after the injection. This monitoring requirement has significantly limited the use of the LAI form. For patients taking an oral dosage of 10-15 mg/day, olanzapine pamoate can be administered monthly (150/300 mg every 2/4 weeks for an oral dosage of 10 mg/day, and 210/405 mg every 2/4 weeks for an oral dosage of 15 mg/day). For individuals switching from an oral dosage of 20 mg/day, olanzapine pamoate should be administered at 300 mg every 2 weeks (Eli Lilly 2021).

Bipolar Disorder and Treatment-Resistant Depression

Before the introduction of SGA medications, traditional antipsychotic medications were well known to be useful in the treatment of mania. Findings from a study assessing the effects of olanzapine versus haloperidol on symptoms of schizoaffective disorder provided a rationale for studying olanzapine in bipolar disorder; in this study, patients who received olanzapine showed superior outcomes on many, but not all, measures compared with patients who received haloperidol (Tran *et al.* 1999).

The first controlled study of olanzapine in bipolar disorder was a 21-day comparison of olanzapine with placebo (Tohen *et al.* 1999). Significantly greater improvement in manic symptoms (as assessed by mean change from baseline to endpoint in Young Mania Rating Scale [YMRS] total score) was observed for patients taking olanzapine compared with those taking placebo. No difference was seen in the outcomes for depression. In this study, EPS were not more frequent in patients taking olanzapine than in those taking placebo (Tohen *et al.* 1999). These findings were confirmed in a second pivotal study that also showed an advantage for olanzapine over placebo (Tohen *et al.* 2000). An open-label follow-up (49 weeks) added valuable information, especially noting that decreases in YMRS scores continued. For the longer term, depression scores also improved. Importantly, for the patients who were exposed to olanzapine at a mean dosage of approximately 14 mg/day, no cases of tardive dyskinesia occurred (Sanger *et al.* 2001).

A question of practical interest is how olanzapine compares with conventional mood stabilizers. In a double-blind trial conducted by Eli Lilly, olanzapine was compared with lithium in the maintenance treatment of bipolar disorder (Tohen *et al.* 2005). Patients were stabilized on a combination of lithium and olanzapine and then randomly assigned to receive one or the other for 52 weeks. In the noninferiority analysis, olanzapine was shown to be as effective as lithium in preventing depression relapse, and the patients given olanzapine had lower rates of mixed or manic symptom relapse over the 52-week follow-up than did those given lithium. Weight gain was higher in the olanzapine group (Tohen *et al.* 2005). Further studies similarly confirmed the equivalent efficacy of olanzapine and divalproex (Tohen *et al.* 2002). This line of research led to FDA approval of olanzapine for the treatment of manic symptoms.

The mean dosage used in olanzapine monotherapy for mania is similar to that used in schizophrenia: 13 mg/day. For acute mania in agitated bipolar patients, intramuscular olanzapine has been shown to be effective (Meehan *et al.* 2001).

The treatment of bipolar depression is often complex. Monotherapy with antidepressants is associated with an increased risk of switching into mania. The OFC is FDA approved for treatment of bipolar depression. In an

8-week double-blind trial conducted by Eli Lilly, OFC was compared against olanzapine monotherapy and placebo in patients with bipolar I disorder in a depressed phase. Although both active treatments were more effective than placebo, OFC was significantly more effective than olanzapine in treating depressive symptoms. By the fourth week of the study, OFC-treated patients showed greater improvement in mood than did olanzapine-treated patients (Tohen *et al.* 2003). Subjects' health-related quality of life also improved (Shi *et al.* 2004). Rates of treatment-emergent mania with OFC were low and did not significantly differ from rates with placebo or olanzapine monotherapy (Amsterdam and Shults 2005; Tohen *et al.* 2003). Recent meta-analyses have shown olanzapine to have a durable benefit for bipolar depression (Bahji *et al.* 2020); however, given the risks associated with olanzapine, the International Society for Bipolar Disorders designates OFC as a second-line agent in its most recent guidelines (Yatham *et al.* 2018).

In adolescents with bipolar I disorder, Tohen *et al.* (2007) reported significantly greater improvement in mania ratings with olanzapine than with placebo. A study conducted by Eli Lilly demonstrated that OFC was superior to placebo in bipolar adolescents in a double-blind RCT (Detke *et al.* 2015). Side effects were similar to those in adults, including changes in glucose and lipids. Both olanzapine and OFC have been FDA approved for bipolar depression in adolescents.

OFC has been studied and FDA approved for use in treatment-refractory major depressive disorder. Thase *et al.* (2007) conducted a study comparing OFC with olanzapine or fluoxetine monotherapy in patients who had not shown adequate response to at least two prior trials of antidepressants. In the pooled analysis (Thase *et al.* 2007), OFC produced greater improvement than olanzapine monotherapy or fluoxetine monotherapy (as assessed by scores on the Montgomery-Asberg Depression Rating Scale [(MADRS]). In a double-blind trial sponsored by Eli Lilly, olanzapine, fluoxetine, OFC, and venlafaxine showed similar rates of efficacy (Corya *et al.* 2006).

Off-Label Uses

Dementia-Related Agitation and Psychosis

Olanzapine does not have an FDA-approved indication for treating elderly patients with dementia and carries a black box warning for use in this population due to increased risk of death, primarily from cardiovascular and infectious complications (U.S. Food and Drug Administration 2011). Professional organizations, including the American Medical Directors Association (2012) and the American Geriatrics Society, recommend against the use of antipsychotics as a first choice to treat behavioral and psychological symptoms of dementia (Rabins *et al.* 2007). However, when agitation is of sufficient severity, and if psychosis is at the root of the agitation--with appropriate discussion of risks and benefits--olanzapine may be a reasonable option (Duong *et al.* 2015).

A large placebo-controlled trial of olanzapine in patients with Alzheimer's disease showed that lower dosages of olanzapine (5-10 mg/day) were significantly better than placebo in treating target symptoms of agitation, hallucinations, and delusions (Street *et al.* 2000). Other trials have since replicated these findings with similar doses (De Deyn *et al.* 2004). A recent comparative meta-analysis was unable to differentiate between the risks and benefits for olanzapine and those for aripiprazole, quetiapine, or risperidone, although olanzapine and risperidone did show increased risk for stroke compared with placebo. Olanzapine also did not differ from placebo on any measures of effectiveness, including the Neuropsychiatric Inventory (NPI), which measures dementia-related behavioral symptoms (Yunusa *et al.* 2019).

Several studies have examined olanzapine in the treatment of dementia without agitation (Brooks and Hoblyn 2007). A placebo-controlled multicenter trial conducted by researchers at Eli Lilly evaluated olanzapine at low fixed dosages (1.0, 2.5, 5.0, and 7.5 mg/day) for treating dementia-related psychosis (De Deyn *et al.* 2004). Although olanzapine did not separate from placebo on the primary outcome measure, the Hallucinations and Delusions items of the NPI Nursing Home edition, improvements were seen in each dosage group studied. All patients who received dosages of 2.5 mg/day or higher were initially started on 2.5 mg/day, with the dosage titrated upward by 2.5 mg/week (as indicated based on assigned study group). There were significant differences from placebo in the acute phase of the study, suggesting that 2.5 mg/day could be an effective starting dosage in acute settings. Regarding secondary outcomes, the most significant improvement was seen with the highest olanzapine dosage (7.5 mg/day), suggesting that up-titrating dosages may be beneficial for some individuals if tolerated. Because no higher dosages were studied, it is unclear whether further increases would lead to greater efficacy (De Deyn *et al.* 2004).

Enhancement of brain levels of acetylcholine has been the focus of treatments aimed at slowing the rate of cognitive deterioration among individuals with dementia. The clinical use of cholinesterase inhibitors is based on that rationale. Olanzapine may have beneficial effects on the regulation of cholinergic and serotonergic neurons that mediate acetylcholine release in the prefrontal cortex. However, in a double-blind study conducted by researchers at Eli Lilly, olanzapine was shown to worsen cognitive functioning, as assessed on the Alzheimer's Disease Assessment Scale for Cognition. Also, there was no statistical difference between the olanzapine and placebo groups in scores on the Clinician's Interview-Based Impression of Change scale (Kennedy *et al.* 2005). Patients in the olanzapine group also showed cognitive worsening on the Mini-Mental State Examination (MMSE). Previous studies found little or no benefit for cognition from olanzapine treatment in non-agitated patients with dementia (De Deyn *et al.* 2004; Street *et al.* 2000).

The CATIE study, which had an Alzheimer's disease component (Schneider *et al.* 2006b; Vigen *et al.* 2011), also compared olanzapine, risperidone, and quetiapine with placebo in the treatment of psychosis and agitation in outpatients. Patients were included if they had psychotic symptoms and resided either in an assisted-living facility or at home. They were excluded if they needed skilled nursing, had primary psychotic disorders, or had previously received cholinesterase inhibitors or antidepressants. As in the schizophrenia portion of CATIE, the primary outcome variable was time to discontinuation. There was no difference among the groups, and no benefit on the Alzheimer's Disease Cooperative Study-Clinical Global Impression of

Change. The average time to discontinuation ranged from 5 to 8 weeks among the treatments. Discontinuation due to lack of efficacy occurred sooner for patients receiving placebo or quetiapine than for those receiving risperidone or olanzapine. Side effects such as parkinsonism, sedation, and increased BMI occurred more frequently with the study medications than with placebo (Schneider *et al.* 2006b; Vigen *et al.* 2011).

Overall, the evidence supporting the effectiveness of SGAs in the treatment of dementia is weak. Olanzapine should not be the first choice when managing dementia-related agitation. Physicians must remember the risks of worsened cognitive function and metabolic dysfunction when prescribing this medication. Current consensus and guidelines agree that evidence for treatment of dementia-related agitation and psychosis with olanzapine is insufficient and recommend against its routine use (Frederiksen *et al.* 2020). Nonetheless, behavioral consequences and patient safety may sometimes require more aggressive treatment, and antipsychotic medication may be warranted. Olanzapine is considered an intermediate-risk antipsychotic in this population (Kales *et al.* 2012). Ultimately, a painstaking evaluation of the risk-benefit ratio for antipsychotic medication use must precede any decision to prescribe these agents in both the short and long terms. Further studies are needed, however, regarding the use of SGA medications in this population (Schneider *et al.* 2006a).

Borderline Personality Disorder

Borderline personality disorder (BPD) is a severe disorder with a U.S.A. point prevalence of 1.6% and a lifetime prevalence of 5.9% (Lenzenweger *et al.* 2007). Earlier studies indicated that low dosages of traditional antipsychotic medications might be useful for symptoms in the psychosis spectrum and overall symptoms of BPD. On the basis of this idea, Schulz *et al.* (1999) conducted an open-label study and found that olanzapine led to substantial improvement in psychoticism, depression, interpersonal sensitivity, and anger (as measured by Hopkins Symptom Checklist-90 ratings), as well as improvement on objective measures of impulsivity and aggression. Of the 11 women enrolled, 9 (82%) completed the study. The trial allowed for early flexible dosing, and the subjects ended their 8 weeks taking an average dose of 7.5 mg/day at bedtime. Zanarini and Frankenburg

(2001) extended this trial and demonstrated olanzapine's (5 mg/day) superiority to placebo over a 26-week study period.

In a study comparing olanzapine, fluoxetine, and a combination of both drugs in women with BPD, olanzapine monotherapy was found to be more effective (as assessed with the MADRS) than either fluoxetine or the olanzapine/fluoxetine combination in treating the depressive symptoms of the disorder. Additionally, olanzapine was superior to fluoxetine in treating symptoms of impulsivity and aggression, as measured by the Overt Aggression Scale. Weight gain was more frequent among olanzapine-treated patients than among patients receiving either of the other two compounds (Zanarini *et al.* 2004).

Two large placebo-controlled studies evaluating olanzapine in BPD yielded mixed results. Schulz *et al.* (2008) reported no significant advantage for olanzapine over placebo in a flexible-dosing design, whereas Zanarini *et al.* (2011) noted a statistical advantage for higher-dosage olanzapine in a fixed-dose trial comparing low-dosage olanzapine, higher-dosage olanzapine, and placebo for 12 weeks. In an open-label 12-week extension phase of the same study, Zanarini *et al.* (2012) found that patients

treated with olanzapine in the initial study maintained the modest improvements in their symptoms. Patients treated with placebo in the initial 12 weeks who were crossed over to olanzapine in the extension phase achieved a level of symptom relief similar to those who had started with olanzapine. These mixed results demonstrate the controversies of using antipsychotic medications in BPD.

Dialectical behavior therapy (DBT) is the mainstay of treatment for BPD. In a double-blind, placebo-controlled trial, olanzapine was studied as an adjunctive agent in patients receiving DBT. Impulsive and aggressive behaviors were found to be lower in the group that received olanzapine than in the placebo group. The average olanzapine dosage in the trial was 8.8 mg/day. Statistically significantly greater increases in weight gain and dyslipidemia were observed in the olanzapine group compared with the placebo group (Soler *et al.* 2005). A similar trial also demonstrated significant improvement in irritability, aggression, depression, and self-inflicted injury for patients in the adjunctive olanzapine group (Linehan *et al.* 2008). It is possible that olanzapine, particularly in conjunction with DBT, may be helpful for treating impulsivity, aggression, and depressive symptoms in BPD; attention to side effects and risks is warranted and ultimately limits use of olanzapine in this population.

Anorexia Nervosa

Anorexia nervosa (AN) is a severe psychiatric illness that carries the highest mortality rate among mental disorders, with a lifetime prevalence between 0.5% and 3% (Campbell and Peebles 2014). Severe restriction of food intake and consequent low weight are primary features of the disorder. Additionally, patients may have psychotic-like disturbances in self-perceived body size or shape, as well as unusual ideas about food and metabolism. Olanzapine was proposed as a treatment adjuvant for this population. Current knowledge largely comes from pilot studies and case series, with some data emerging from small, controlled trials.

In an open-label trial, 17 patients hospitalized for AN were given olanzapine in addition to cognitive-behavioral therapy (CBT) and DBT. Olanzapine's initial dosage of 1.25-5.00 mg/day was titrated upward as needed, balancing efficacy against side effects. Patients showed improvement in weight and Beck Depression Inventory and Spielberger State-Trait Anxiety Inventory scores, but the lack of a control group limited the validity of these results (Barbarich *et al.* 2004). A randomized trial in which 15 women with AN were assigned to either olanzapine or chlorpromazine in a balanced block design found that olanzapine reduced anorexic ruminations (as measured by the impaired control over mental activities subscale of the Padua Inventory). There was no difference in weight gain between the two groups. However, this study was limited by its nonblinded design (Mondraty *et al.* 2005). A case series evaluating low-dosage olanzapine treatment in 13 adolescent girls with restricting-type AN reported weight increase and lower hyperactivity in the 7 girls who responded to olanzapine (response was defined as improvement of at least 50% on the Eating Attitudes Test-26) (Leggero *et al.* 2010).

Results of double-blind RCTs are mixed. In a 10-week trial of 34 women with AN, Bissada *et al.* (2008) found significant increases in weight and reductions in obsessive symptoms among those treated with olanzapine. Similarly, in an 8-week study of 23 outpatient women with AN, end-of-treatment BMI was greater among women receiving olanzapine than those receiving placebo. Psychological symptoms improved

equally in both groups (Attia *et al.* 2011). However, a trial of olanzapine versus placebo in 20 adolescent girls with AN found no differences in median body weight at either week 5 or week 10. The two groups showed similar improvements in eating attitudes, psychological functioning, and resting energy expenditure (Kafantaris *et al.* 2011).

Most recently, in a double-blind RCT, 152 adult outpatients diagnosed with AN were randomly assigned to either olanzapine or placebo treatment over 16 weeks. Weight gain and obsessive traits were the primary outcomes of this study. Obsession was rated by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Patients in the olanzapine treatment group had statistically significantly greater gains in weight but no differences in psychological symptoms compared with the placebo group (Attia *et al.* 2019).

Given that weight gain is a prominent side effect of olanzapine, studies are examining the mechanisms underlying this effect and the possibility that olanzapine might be useful as a weight-gain agent. In a double-blind, placebo-controlled trial, Brambilla *et al.* (2007) investigated whether olanzapine might induce weight gain through modulation of ghrelin and leptin (hormones associated with satiety). Patients with AN received olanzapine or placebo with CBT, and their levels of ghrelin and leptin were assessed over 3 months. Patients in both the olanzapine and placebo groups had increased weight, but there was no statistical difference between the groups regarding weight gained or levels of leptin or ghrelin, which remained unchanged over the course of the study.

The role of olanzapine as an augmentation to psychotherapy in AN is limited at best. Most high-quality studies did not find psychological or physical improvement for patients treated with the drug. However, there may be a limited role for olanzapine in patients for whom timely weight gain is medically imperative and urgent. Since the trials thus far have been small and the results mixed, further research is required to clarify this matter.

Posttraumatic Stress Disorder

PTSD is characterized by disproportionate and disturbing symptoms of fear persisting for longer than 1 month following a severe trauma. In some cases, psychosis can occur, leading to intense feelings of horror and helplessness. This phenomenon led investigators to consider a potential role for olanzapine in the treatment of PTSD, although available data are still limited.

In a double-blind, placebo-controlled augmentation trial of olanzapine in 19 patients with PTSD who were minimally responsive to 12 weeks of selective serotonin reuptake inhibitor (SSRI) treatment, olanzapine produced limited symptomatic improvements compared with placebo on measures of PTSD, depression, and sleep. However, clinician-rated overall clinical response rates did not differ between the groups. Patients receiving olanzapine had an average weight gain of 13 lb (Stein *et al.* 2002).

An open-label study compared olanzapine versus fluphenazine as monotherapy for 6 weeks in male patients with combat-related PTSD and psychosis. Olanzapine was significantly more efficacious in reducing symptom scores on the PANSS (negative, general, psychopathology subscale, supplementary items), Watson's PTSD subscales (avoidance, increased arousal), and a variety of global impression scales (Clinical Global Impression Severity and Improvement scales and Patient Global Impression Improvement [PGI-I] scale) at 3 and 6 weeks. The two medications produced similar improvements on PANSS positive and Watson's trauma reexperiencing subscale scores. An additional 3 weeks of treatment did not increase symptom improvements for either drug (Pivac *et al.* 2004).

A small double-blind RCT studied patients with non-combat-related PTSD. Patients in this study who received olanzapine demonstrated significantly greater improvement on the Clinician-Administrated PTSD

Scale over 8 weeks of treatment compared with those who received placebo (Carey *et al.* 2012). This was the most recent trial looking into this association, and no ongoing trials currently are registered on clinicaltrials.gov. Hence, evidence supporting the use of olanzapine in PTSD is weak at best.

Obsessive-Compulsive Disorder

OCD is characterized by recurrent, unwanted, and anxiety-inducing obsessive thoughts and the repetitive behaviors compulsively performed as an attempt to ease those thoughts. At times, obsessions are so disconnected from reality that they resemble psychosis. A few double-blind, placebo-controlled clinical trials have examined olanzapine's potential efficacy in augmentation of traditional SSRI treatment of OCD.

One trial enrolled 26 patients who had not responded to traditional SSRI therapy. Patients received olanzapine or placebo augmentation for 6 weeks and were assessed biweekly with the Y-BOCS. Six (46%) of the 13 olanzapine-treated patients showed clinical response (defined as a 25% or greater reduction on Y-BOCS scores), versus none in the placebo group (Bystritsky *et al.* 2004). In a second trial, poor responders to fluoxetine received an additional 6 weeks of either olanzapine or placebo augmentation. Both groups improved, but there were no differences between groups in the extent or timing of improvement as measured by Y-BOCS scores (Shapira *et al.* 2004).

More recent studies suggest that olanzapine is effective in only a limited set of patients with OCD, mainly those with hoarding or symmetry-based symptoms. Available data do not support olanzapine as a first-line drug for OCD (Matsunaga *et al.* 2009). Given the mixed results and small sample sizes of the existing studies, further research is needed to establish possible benefits of olanzapine augmentation for OCD. Currently, no registered ongoing clinical trials are looking into this association.

Delirium

Delirium is a neuropsychiatric syndrome characterized by acute and fluctuating changes in mental status, circadian rhythm, and cognition. It is generally attributed to underlying medical conditions, such as infections, hydroelectrolytic disorders, and CNS perturbations. Delirium is a marker of poor clinical outcomes because it is associated with cognitive decline, prolonged hospitalization, institutionalization, personal and caregiver suffering, and a higher risk of death (Inouye *et al.* 2014). With an estimated prevalence of 20% in hospitalized adults, 50% in mechanically ventilated patients, and up to 70% in inpatient palliative care patients (Gibb *et al.* 2020), there is high interest in the treatment of this condition. Several RCTs and open trials have studied the role of olanzapine as an adjuvant in the management of delirium.

Larsen *et al.* (2010) compared the efficacy of 10 mg of orally disintegrating olanzapine versus placebo in a prophylaxis trial. Their population consisted of 400 elderly persons ages 65 years and older undergoing elective knee or hip replacement surgeries. A 5-mg pill was given just before and just after surgery. The olanzapine group had a lower rate of delirium, in both types of surgery. However, for those patients who developed the disorder while taking olanzapine, it lasted longer and was more severe.

Yoon *et al.* (2013) compared haloperidol, risperidone, olanzapine, and quetiapine in the treatment of delirium in an inpatient setting. Outcomes were measured with the Korean version of the Delirium Rating Scale-Revised 98 (DRS-K) and the MMSE. A total of 80 patients were evenly distributed among the four groups; there were no differences in baseline DRS-K and MMSE scores. All groups had similar rates of improvement, and there were no significant differences in subscale scores. The response rate was lower in individuals older than 75 years, regardless of the group. Also, there were no differences in side-effect profiles. Grover *et al.* (2011) previously performed a similar comparison of olanzapine, risperidone, and olanzapine and also did not find any differences among the groups.

Jain *et al.* (2017) performed an open-label RCT with 100 patients admitted to different medical wards. Delirium was assessed with the Confusion Assessment Method Scale. Patients were given haloperidol (1-4 mg/day) or olanzapine (2.5-10 mg/day). Outcomes included improvement in symptom scores on the Memorial Delirium Assessment Scale and rate of extrapyramidal side effects on the Simpson Angus Scale. Both groups had similar symptomatic improvements, with no differences in side effect occurrence. Lin *et al.* (2008) previously performed a similar comparison of haloperidol and olanzapine and found no differences between the groups.

As of now, data support the role of antipsychotics as an adjuvant in the management of delirium. We highlight that investigating and treating the underlying cause should always be the priority. There seem to be no differences between olanzapine and other commonly used antipsychotics.

Nausea and Vomiting

Guidelines established by the American Society of Clinical Oncology (ASCO) (Hesketh *et al.* 2017) and the National Comprehensive Cancer Network (2018) already recommend olanzapine as an adjuvant in the management of chemotherapy-induced nausea. In this context, patients benefit from the quadruple combination of olanzapine 10 mg, a 5-HT_3 receptor antagonist, a neurokinin$_1$ (NK_1) receptor antagonist, and dexamethasone. Smaller doses could be used for patients older than 75 years to reduce the age-related risk of sedation. Hashimoto *et al.* (2020) conducted a multicenter double-blind RCT to evaluate the efficacy of olanzapine 5 mg added to triplet-combination antiemetic therapy (i.e., aprepitant, palonosetron, and dexamethasone) as a standard of treatment against highly emetogenic chemotherapy agents.

In the past decade, several other clinical trials investigated the efficacy of olanzapine for chemotherapy-induced nausea. Navari *et al.* (2011, 2016, 2020), Tienchaiananda *et al.* (2019), Clemmons *et al.* (2018), Babu *et al.* (2016), Wang *et al.* (2015), Mizukami *et al.* (2014), and L. Tan *et al.* (2009) conducted similarly structured trials that support current guidelines. In all studies, olanzapine-treated patients had greater reductions in nausea and emesis when compared with placebo. Additionally, with results similar to those of Hashimoto *et al.* (2020), all studies that looked at olanzapine as adjunctive therapy also favored the quadruple combination strategy, with dosages varying from 5 mg to 10 mg/day.

The role of olanzapine in the treatment of non-oncological nausea and vomiting has not been studied, and therefore, no other recommendations can be made at this point.

Side Effects and Toxicology

Neurological and Extrapyramidal Adverse Effects

Adverse effects of olanzapine reported in clinical use are consistent with findings in preclinical studies, which predicted few neurological effects. In Phase II and III clinical trials, olanzapine-treated patients generally showed an improvement in EPS from baseline, reflecting the fact that most of the subjects had previously taken first-generation antipsychotics. In a large multinational comparison study (Tollefson *et al.* 1997), olanzapine produced fewer treatment-emergent neurological adverse effects than haloperidol, including parkinsonism (14% vs. 38%) and akathisia (12% vs. 40%). In a comprehensive meta-analysis, the relative risk (RR) of EPS for olanzapine was 0.39 compared with haloperidol (Leucht *et al.* 2009).

Antiparkinsonian medication is sometimes required when patients are treated with olanzapine, although the need for such medication is generally lower with olanzapine than with antipsychotics having greater potency at the D_2 receptor. In one study (Volavka *et al.* 2002), antiparkinsonian agents were prescribed to 13% of both clozapine-treated and olanzapine-treated subjects, compared with 32% of risperidone-treated patients. In a meta-analysis of RCTs, Komossa *et al.* (2010) found that olanzapine incurred a modestly higher risk of EPS (as measured by use of antiparkinsonian medication) compared with quetiapine (RR, 2.05) but a lower EPS risk compared with risperidone (RR, 0.78) and ziprasidone (RR, 0.70).

Evidence now exists for phenotypic variation in the risk of EPS among olanzapine-treated patients. A meta-analysis of 4,831 subjects compared the incidence of olanzapine-induced EPS in patients with schizophrenia versus patients with bipolar disorder. Parkinsonism was significantly higher among schizophrenia patients (13.9% vs. 3.1%), and this difference remained significant after adjustment for gender. There were no differences between groups on measures of akathisia or use of antiparkinsonian medication (Moteshafi *et al.* 2012).

The reduction of EPS is predictive of decreased risk of tardive dyskinesia, the most problematic of the common adverse effects of classic antipsychotics. Accumulated experience with SGAs indicates that tardive dyskinesia is 10-to 15-fold less common with these agents than with conventional agents, with an annual rate of 0.52% in olanzapine-treated patients compared with 7.45% in haloperidol-treated patients, based on pooled data from long-term comparison trials (Beasley *et al.* 1999). Miller *et al.* (2008) examined data from the previously described CATIE study; after excluding subjects who met criteria for tardive dyskinesia at baseline, they found no difference in incidence of tardive dyskinesia over 1 year between patients treated with olanzapine and patients treated with any other antipsychotic (perphenazine, quetiapine, risperidone, or ziprasidone).

Weight Gain and Other Metabolic Effects

Weight gain and associated dyslipidemia are among the most significant major adverse effects found during treatment with olanzapine. Weight gain is a serious concern because persons with schizophrenia are more likely than the general population to be obese, and weight gain may contribute to nonadherence to antipsychotic treatment, leading to increased risk for relapse. With the reduced risk of neurological side effects attached to SGAs, metabolic effects have emerged as a major risk for patients and a focus of consideration for clinicians.

Recent studies have attempted to find the cause of metabolic dysregulation associated with antipsychotic drugs. Aslanoglou *et al.* (2021) demonstrated that human and mouse pancreatic a- and b-cells express the catecholamine biosynthetic and signaling machinery and that a-cells synthesize dopamine de novo. This locally produced pancreatic dopamine signals via both a- and b-cell adrenergic and dopaminergic receptors with different affinities to regulate glucagon and insulin release. The investigators additionally found that dopamine functions as a biased agonist at a_{2A}-adrenergic receptors, preferentially signaling via the canonical G protein-mediated pathway. This ability of dopamine to signal differently on dopaminergic receptors versus adrenergic receptors may be critical for fine-tuning the regulation of blood sugar, which is essential for life. Aslanoglou *et al.* (2021) also showed that pharmacological blockade of D_2-like receptors in human islets with antipsychotic drugs significantly raises insulin and glucagon release. These findings provide new mechanisms to explain how antipsychotics act directly on islet a- and b-cell targets to produce metabolic disturbances (Aslanoglou *et al.* 2021).

The relative degree of weight gain associated with 18 antipsychotics was studied in a comprehensive meta-analysis by Pillinger *et al.* (2020). With a combined total of nearly 26,000 research subjects in 100 clinical trials (median duration 6 weeks), they replicated the classic work of Allison *et al.* (1999) showing that olanzapine and clozapine were the most likely antipsychotics to cause weight gain. These findings were also seen in long-term follow-up data (Kishimoto *et al.* 2019).

The treatment of olanzapine-induced metabolic dysfunction mirrors the treatments offered for weight gain or insulin resistance/diabetes in general. Lifestyle interventions should be the first line, with exercise (three times per week for 30 minutes to start) and a balanced, healthy diet focusing on whole grains, leafy green vegetables, and lean proteins (Vancampfort *et al.* 2019). Beyond that, there is a role for medication. Most well studied has been metformin, an agent known to decrease hepatic glucose output. Although not typically a weight-loss agent, metformin has been used both for its normoglycemic properties and to prevent or treat weight gain associated with olanzapine use. Investigators from the Use of Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia Study randomly assigned 148 clinically stable overweight outpatients with schizophrenia or schizoaffective disorder to up to 2,000 mg of metformin or placebo daily (Jarskog *et al.* 2013). Patients were taking either one or two of any of the FDA-approved antipsychotic medications. All patients received weekly diet and exercise counseling. After 16 weeks, patients taking metformin had lost significantly more weight than those taking placebo (6.6 lb vs. 2.2 lb). The metformin group also showed significant reductions in triglyceride levels ([?] 7.0 mg/dL vs. + 13.2 mg/dL) and modest reductions in hemoglobin A1C, a measure of elevated blood glucose ([?] 0.06% vs. + 0.011%), with a time x treatment interaction, suggesting that the benefits of metformin increase with time. There were no significant differences in fasting glucose or insulin levels (Jarskog *et al.* 2013). More recently, glucagon-like peptide 1 (GLP-1) agonists have begun to show promise in countering the weight-gain effects of olanzapine, with more studies ongoing and newer GLP-1 agonists in development (Siskind *et al.* 2019). Other drugs associated with weight loss, including topiramate and a bupropion/naltrexone combination, have either failed to show efficacy or are limited by intolerable side effects in sufficient numbers to limit their utility.

In a double-blind, placebo-controlled trial in adolescents who had gained weight after 1 year of treatment with an SGA (olanzapine, risperidone, or quetiapine), the addition of metformin resulted in statistical reductions in waist circumference and BMI and stabilization of weight gain (Klein *et al.* 2006). Homeostatic Model Assessment for Insulin Resistance scores were significantly decreased and the number of subjects requiring referral for a glucose tolerance test was reduced among patients who received metformin. A subsequent meta-analysis has shown that weight benefits in adolescents come after 4 weeks of treatment, but due to concerns with the quality of the component clinical trials, more work is needed to definitively conclude a benefit from metformin (Ellul *et al.* 2018).

Weight gain is an even greater concern in the treatment of children and adolescents, who are more likely to be experiencing an initial exposure to antipsychotics and thus are more prone to rapid metabolic changes (Ballon *et al.* 2014). In a network meta-analysis of 28 RCTs, olanzapine showed significantly more weight gain compared with other antipsychotics in children and adolescents (Krause *et al.* 2018). These findings replicated the patterns seen in adults with regard to side effects.

Changes in weight, lipids, and insulin metabolism raise serious concerns for diabetes and related complications. Olanzapine is linked to both weight gain and insulin resistance and may cause both independently (Ballon *et al.* 2014). Just as in weight gain, olanzapine and clozapine have been consistently shown to pose the greatest risk for insulin resistance and diabetes (Zhang *et al.* 2017).

The accumulation of metabolic risk factors presents a great clinical conundrum in regard to olanzapine and clozapine. Although these drugs have been shown in the CATIE and other studies to have clinical superiority for antipsychotic effect, the metabolic side effects are so limiting as to make olanzapine a second-line agent in many cases. With FDA approval of the olanzapine/samidorphan combination in 2021 (Alkermes 2021), this may change, because the risk of weight gain is lower after 6 weeks of treatment (Correll *et al.* 2020). Results in early psychosis are still pending, however, and the overall metabolic impact other than weight gain has thus far not shown a significant difference. As this medication becomes available for wide-scale clinical use, further research will be warranted to determine whether use of this combination will make olanzapine a more attractive agent for use in the treatment algorithm.

In addition to the opioid antagonist approach to managing antipsychotic-induced weight gain, there is another mechanism under investigation utilizing glucocorticoid receptor antagonism. It has been shown that dysregulation of the hypothalamic-pituitary-adrenal axis has been implicated with the use of atypical antipsychotics (Baptista *et al.* 2004). A proof-of-concept study enrolled 66 healthy men in a 2-week double-blind RCT of miricorilant, an investigational mixed agonist/antagonist of the glucocorticoid receptor and a mineralocorticoid receptor antagonist with no progesterone activity that has shown efficacy in a rat model of olanzapine-induced weight gain (Hunt *et al.* 2021). Subjects who received olanzapine + miricorilant gained less weight than those given olanzapine + placebo (mean weight gain on day 15, 3.91 kg vs. 4.98 kg; difference between groups, [?] 1.07 kg; 95% CI, [?] 1.94 to [?] 0.19; P = 0.017). Compared with placebo, coadministration of miricorilant with olanzapine was associated with smaller increases in insulin, triglycerides, aspartate aminotransferase, and alanine aminotransferase. Two Phase II studies of miricorilant in patients with recent and long-standing antipsychotic-induced weight gain are currently in progress (NCT03818256 and NCT04524403).

There have been additional studies using mifepristone, a glucocorticoid receptor and progesterone receptor antagonist, showing similar results in rats and healthy adults (Beebe *et al.* 2006; Gross *et al.* 2009). The selective glucocorticoid receptor antagonism mechanism of CORT125281 has been studied in comparison with nonselective mifepristone in a mouse model for diet-induced obesity in which rhythmicity of circulating corticosterone levels was disturbed. The study showed that both compounds reduced body weight gain and fat mass; however, only CORT125281 restored the disturbed rhythmicity; lowered plasma levels of triglycerides, cholesterol, and free fatty acids; and strongly stimulated triglyceride-derived fatty acid uptake by brown adipose tissue depots (Kroon *et al.* 2018).

Other Side Effects

Among other side effects reported with olanzapine, sedation is frequent at the start of therapy but diminishes as patients develop tolerance for this side effect. In long-term treatment, the incidence of sedation is about 15%, similar to that of haloperidol. Prolactin elevations observed during olanzapine treatment occur early in treatment, and levels are much lower than those seen with risperidone or typical antipsychotics. Leukopenia is rare and occurs at a rate similar to that seen with other first-and second-generation antipsychotics, but olanzapine does not cause agranulocytosis, even in patients who developed this effect while taking clozapine. In animal toxicology studies and in clinical trials of olanzapine, no QTc prolongation was observed, and other cardiovascular effects were rarely of clinical importance (Cadario 2000).

Safety in Overdose

Reviews of case series and reports of olanzapine toxicity in adults describe predominantly circulatory and CNS effects, including coma, psychomotor agitation, hypertension and hypotension, tachycardia and bradycardia, hyperthermia and hypothermia, miosis and mydriasis, and QTc prolongation (QTc prolongation only with > 1,040 mg ingestion and in mixed overdoses) (Ciszowski *et al.* 2011; H. H. Tan *et al.* 2009). Olanzapine overdose was rarely fatal in the aforementioned case reports, and a systematic study of SGA overdose found that of 422 olanzapine overdoses, there were no fatalities, and 14% of patients required ventilation (Berling *et al.* 2016). Supportive care and careful cardiac, respiratory, and neurological monitoring for anticholinergic toxicity is generally the extent of treatment of olanzapine overdose, but a recent case report suggested using physostigmine to help diagnose and treat the toxidrome of olanzapine overdose (Serrano and Maldonado 2021). Very few data describe olanzapine overdose in children; available case report data are consistent with adult presentations of EPS and elevated prolactin levels (Tanoshima *et al.* 2013) and circulatory and neurological symptoms (McAllister *et al.* 2012).

Use in Pregnancy

The decision whether to continue use of olanzapine during pregnancy is important and complex for each individual. Potential risks of exposure must be balanced against the risks of relapse during and immediately after pregnancy. Exposure to olanzapine

was associated with a modest increase in risk of gestational diabetes in an analysis of Medicaid records (RR, 1.61), with 12% of women who stayed on olanzapine developing gestational diabetes compared with 4.7% of women who stopped olanzapine. This was a higher risk than with other antipsychotic drugs (Park *et al.* 2018). Overall, there is not an increased rate of birth defects for olanzapine (Betcher and Wisner 2020).

Drug-Drug Interactions

Olanzapine is metabolized primarily via glucuronidation and via oxidation by CYP1A2 (see "Pharmacokinetics and Disposition" earlier in this chapter). Other drugs that affect the activity of these metabolic pathways would therefore be expected to affect olanzapine pharmacokinetics. Indeed, drugs that inhibit CYP1A2 activity have been shown to decrease olanzapine clearance, thereby increasing olanzapine plasma concentrations.

Fluvoxamine, a known inhibitor of CYP1A2, has been shown to inhibit olanzapine metabolism in several studies. In an 11-day study of 10 healthy male smokers, coadministration of fluvoxamine (50-100 mg/day) with olanzapine (2.5-7.5 mg/day for 8 days [beginning on day 4]) resulted in an 84% increase in olanzapine peak serum concentrations (C_{max}) and a 119% increase in area under the plasma concentration-time curve over the last 24-hour dosing interval (AUC_{0-24}) compared with placebo coadministered with olanzapine. No change in half-life was observed in either olanzapine or 4'-*N*-desmethylolanzapine, suggesting that fluvoxamine inhibited olanzapine's first-pass metabolism (Maenpaa *et al.* 1997).

Fluoxetine and imipramine, although not known to be significant inhibitors of CYP1A2, when coadministered with olanzapine have been associated with small but statistically significant changes in olanzapine pharmacokinetics. Coadministration of fluoxetine with olanzapine resulted in a 15% decrease in olanzapine clearance and an 18% increase in C_{max}, with no significant difference in olanzapine half-life (Callaghan *et al.* 1999). Coadministration of imipramine with olanzapine resulted in an approximately 14% increase in olanzapine C_{max} and a non-statistically significant increase in olanzapine AUC of 19% (Callaghan *et al.* 1997).

Inducers of the CYP1A2 enzyme increase olanzapine clearance, thereby decreasing olanzapine systemic exposure. Carbamazepine, an inducer of several CYP enzymes (including CYP1A2), affects olanzapine disposition. A study in healthy volunteers reported that a single 10-mg dose of olanzapine taken after 2 weeks of pretreatment with carbamazepine (200 mg twice daily) had significantly higher clearance and apparent volume of distribution--but significantly lower C_{max}, AUC, and half-life--compared with a single 10-mg dose taken before carbamazepine treatment (Lucas *et al.* 1998).

Smoking, either tobacco or cannabis, is also known to induce CYP1A2 and can affect olanzapine disposition. The polycyclic aromatic hydrocarbons in smoke are responsible for inducing hepatic enzymatic metabolism (Desai *et al.* 2001). For this reason, dosage adjustments may be needed when a patient who smokes is placed in a smoke-free inpatient unit, even if adequate nicotine replacement is provided. Patients who decide to convert to noncombustible methods (e-cigarettes, vapes, edibles) will have a similar change in their olanzapine metabolism. Conversely, when there is a sudden increase in cigarette consumption (often associated with stress or impending relapse), a dosage increase may be needed to prevent an abrupt worsening of symptoms. A study comparing 19 male smokers with 30 male nonsmokers found that olanzapine clearance in smokers was 23% higher than that in nonsmokers (Callaghan *et al.* 1999). A population pharmacokinetic analysis of 910 patients receiving olanzapine found that drug clearance among nonsmokers was 37% lower in men and 48% lower in women than it was in the corresponding group of smokers (Patel *et al.* 1996). In vitro studies suggest that olanzapine does not significantly inhibit the activity of CYP1A2, CYP3A, CYP2D6, CYP2C9, or CYP2C19 (Ring *et al.* 1996a). In vivo studies suggest that olanzapine does not affect the disposition of aminophylline (Macias *et al.* 1998), diazepam, alcohol, imipramine (Callaghan *et al.* 1997), warfarin, biperiden, or lithium (Callaghan *et al.* 1999).

Conclusion

From review of the research focused on olanzapine, this compound, which has been approved for use in the United States since 1997, clearly has wide utility and some distinct advantages compared with traditional antipsychotics. In addition to its positive effects on a broad group of symptoms in schizophrenia, olanzapine is approved for the treatment of mania, both acute and long term, in bipolar disorder. Recent research has shown that olanzapine may be beneficial for disorders beyond psychosis (e.g., BPD, AN, PTSD, OCD). Olanzapine's high clinical efficacy and low risk of dystonia, parkinsonism, and tardive dyskinesia initially led to its greater acceptability in chronic schizophrenia and has encouraged clinicians to prescribe it for other conditions. The extension of olanzapine's uses is, in many ways, made possible by its low rate of movement disorders but is limited by significant metabolic concerns.

Olanzapine is not free from adverse effects; in addition to metabolic toxicity, there is also sedation, hypotension, and the black box warning regarding use in elderly patients limiting its use in some individuals. For this reason, olanzapine is not generally recommended as a first-line agent beyond the acute setting. However, its clinical utility toward the resolution of psychotic symptoms has prompted a significant effort to understand how to mitigate the metabolic side effects. Accordingly, the recently approved olanzapine/samidorphan combination, as well as new adjunctive weight-loss agents such as GLP-1 agonists, may allow olanzapine to be used more safely, thus affording more patients the opportunity to benefit from its clinical efficacy.

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CHAPTER 28

Quetiapine

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History and Discovery

Quetiapine is a second-generation antipsychotic (SGA) developed and subsequently marketed by AstraZeneca. In preclinical trials, quetiapine showed the features associated with antipsychotic efficacy and a low rate of motor effects (Goldstein 1999; Nemeroff *et al.* 2002). Quetiapine was approved in 1997 by the FDA for the treatment of schizophrenia; it was subsequently approved in Europe and in other countries worldwide. Additional approvals and indications for quetiapine's use in bipolar disorder, as well as approval of an extended-release (XR) formulation of quetiapine, have followed (Moller *et al.* 2007; Peuskens *et al.* 2007). The XR formulation has an additional indication as adjunctive treatment for major depressive disorder (MDD) for patients who show inadequate response to antidepressants alone.

Structure-Activity Relations

Quetiapine is an SGA of the dibenzothiazepine class (Figure 28-1). Its complex neuropharmacology includes a low binding profile for dopamine type 2 (D_2) receptors (Kapur *et al.* 2000). Indeed, given that an antipsychotic must occupy 60% or more of D_2 receptors to be clinically efficacious (Kapur *et al.* 2000), quetiapine's low D_2 binding--typically, approximately 30%--is noteworthy.

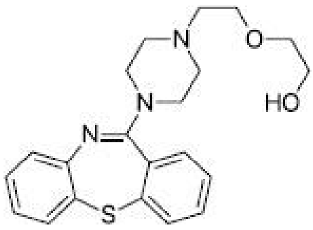

FIGURE 28-1. Chemical structure of quetiapine.

Source. PubChem Compound Database, National Center for Biotechnology Information. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/5002#section=2D-Structure.

In attempting to reconcile this apparently subtherapeutic D_2 receptor antagonism with the well-recorded efficacy of quetiapine as an antipsychotic, Kapur *et al.* (2000) proposed an elegant *kiss and run hypothesis* to explain quetiapine's mechanisms of action. In a series of studies, they found that when D_2 receptor occupancy with quetiapine was measured with PET at shorter intervals (4 hours and 6 hours) than the conventional 12 hours after the last dose was taken, quetiapine did indeed show high D_2 occupancy. In contrast to other antipsychotics, quetiapine demonstrated a more rapid "run-off" from D_2 receptors; that is, there was rapid dissociation of the D_2 receptors (Kapur *et al.* 2000).

Like clozapine, quetiapine has strong binding at the 5-hydroxytryptamine (serotonin) type 2 (5-HT_2) receptors. This profile contrasts with its weak affinity for other subclasses of the serotonin receptor family (Nemeroff *et al.* 2002). Quetiapine also has strong affinity for a_1-noradrenergic receptors. This antagonism may relate to its propensity to induce postural hypotension, especially during rapid dosage titration. Additionally, quetiapine has strong antagonism at histamine type 1 (H_1) receptors. This probably relates to its sedative effect. H_1 receptor antagonism also appears to be a key contributor to weight gain during quetiapine therapy (Kim *et al.* 2007).

Pharmacokinetics and Disposition

Quetiapine is available in oral tablet formulations only (i.e., an immediate-release [IR] tablet and an extended-release [XR] tablet); there are no liquid or intramuscular preparations. Patients receiving IR tablets may be switched to the XR tablet at the equivalent total daily dosage, taken once daily. Individual dosage adjustments may be necessary (AstraZeneca 2020).

Quetiapine IR tablets may be taken with or without food (AstraZeneca 2020). The XR tablets should be taken either without food or with a light meal (500 calories). For the IR tablet formulation, peak blood levels are achieved in about 2 hours, with effective plasma levels sustained for approximately 6 hours (DeVane and Nemeroff 2001). The XR tablet reaches peak concentrations in about 6 hours. Although these pharmacokinetics provide the basis for the usual clinical regimen of twice-daily dosing, a short-term pilot study comparing once-daily dosing versus twice-daily dosing of the IR tablets demonstrated that the two regimens were equivalent in terms of efficacy and tolerability (Chengappa *et al.* 2003b). A PET study (Mamo *et al.* 2008) found comparable plasma levels and D_2 receptor occupancy between the IR and the XR formulation.

Quetiapine is metabolized by cytochrome P450 (CYP) 3A4 to inactive metabolites. The elimination half-life is about 7 hours, and steady state is reached within 2 days. Elderly patients may require a dosage reduction because oral clearance of quetiapine is reduced by about 40% in this population. Quetiapine dosages may need adjustment in the presence of liver disease (AstraZeneca 2013). Quetiapine has a major active metabolite, norquetiapine, with a half-life of approximately 12 hours at clinical dosages.

Coadministration of quetiapine with drugs that alter CYP3A4 activity is likely to result in clinically significant interactions. For example, the anticonvulsants carbamazepine and phenytoin are CYP3A4 inducers, and in their presence quetiapine dosages may need to be increased because of accelerated drug clearance (Potkin *et al.* 2002a, 2002b; Strakowski *et al.* 2002). Ritonavir, erythromycin, ketoconazole, and nefazodone are potent inhibitors of CYP3A4, and their concomitant use with quetiapine requires caution.

Clinical trials (Kahn *et al.* 2007; Lindenmayer *et al.* 2008) comparing the efficacy and tolerability of the XR formulation with the IR formulation indicated that quetiapine XR given once daily (at dosages of 400-800 mg/day) was effective for the treatment of schizophrenia and, on average, was similar in efficacy and tolerability to treatment with quetiapine IR. Similarly, it has been reported that XR and IR formulations achieve comparable efficacy for patients with bipolar disorder (Kishi *et al.* 2019). Regarding dosing of quetiapine, dosages for schizophrenia and mood disorder are similar, and lower dosages of quetiapine are typically reported in off-label use conditions such as anxiety disorders. A dose-response review of antipsychotics for schizophrenia suggested that 482 mg/day was the 95% effective dosage for quetiapine (Leucht *et al.* 2020). The quetiapine dosage equivalent to risperidone 1 mg/day was estimated at 77 mg/day. Quetiapine is excreted in the kidneys and is not affected by the individual's sex or smoking status. The metabolism of quetiapine is reduced by approximately 30% with advancing age (Goldstein 1999).

Indications and Efficacy

Quetiapine in the XR and IR formulations is FDA approved for the following indications in adults: treatment of schizophrenia; acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex; acute treatment of depressive episodes associated with bipolar I or II disorder; and maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex. The XR formulation is also approved for use as an adjunct to antidepressant therapy in the treatment of MDD in adults.

In addition, quetiapine is efficacious in the treatment of schizophrenia and bipolar disorder in pediatric populations (Barzman *et al.* 2006; DelBello *et al.* 2007; McConville *et al.* 2000). The IR formulation is FDA approved for the treatment of schizophrenia in adolescents (ages 13-17 years) and the acute treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents (ages 10-17 years).

There are also reports of quetiapine's efficacy in treating anxiety disorders, OCD, borderline personality disorder, and Parkinson's disease. These uses have not been approved by the FDA. The use of any medication (in this case quetiapine) outside FDA-approved indications is not recommended in clinical practice.

Schizophrenia

Registration and early trials of quetiapine (Arvanitis and Miller 1997; Borison *et al.* 1996; Copolov *et al.* 2000; King *et al.* 1998; Peuskens and Link 1997; Small *et al.* 1997) demonstrated that quetiapine is an efficacious antipsychotic for the treatment of schizophrenia. Short-term (6-week) trials compared quetiapine, haloperidol, and placebo by using quetiapine at flexible daily dosages of [?] 250 mg or [?] 750 mg (Small *et al.* 1997) or fixed daily dosages of 75 mg, 150 mg, 300 mg, 600 mg, or 750 mg (Arvanitis and Miller 1997); the latter trial found that 300 mg/day was superior (but not statistically significantly so) to the lower and higher dosages and was the only dosage demonstrating efficacy for negative symptoms (Arvanitis and Miller 1997). These studies established a range of effective dosages for quetiapine and also suggested that dosages of [?] 250 mg/day were superior to lower dosages.

Subsequent studies helped refine quetiapine dosing strategies. An 8-week fixed-dosage comparison trial of quetiapine at 600 mg/day versus haloperidol at 20 mg/day showed similar efficacy for the two drugs for patients who were partial responders to first-generation antipsychotics (Emsley *et al.* 2000). A study comparing a rapid titration strategy (beginning at 200 mg/day, increasing to 800 mg/day by day 4) with a more conventional dosing strategy (50 mg/day on day 1, increasing up to 400 mg/day by day 5) showed similar efficacy and tolerability for the two strategies (Pae *et al.* 2007). Growing evidence from more recent studies (Honer *et al.* 2012; Lindenmayer *et al.* 2011) discourages the use of very-high-dosage quetiapine, and data are still lacking to indicate that dosages above 300 mg/day are more efficacious.

Most studies comparing quetiapine with either a first-generation antipsychotic or another SGA have reported similar efficacy for the agents in treating schizophrenia (Emsley *et al.* 2000; Peuskens and Link 1997; Small *et al.* 1997). A 4-month open-label trial of quetiapine and risperidone showed overall comparability between the two agents (Mullen *et al.* 2001). An 8-week comparative trial of quetiapine (with an average dosage of 525 mg/day) and risperidone (with an average dosage of 5.2 mg/day) also found the drugs similar in efficacy (Zhong *et al.* 2006). Quetiapine-treated patients had fewer extrapyramidal side effects (EPS), lower prolactin levels, and fewer sexual side effects. Whereas weight gain was similar in both treatment groups, quetiapine was more sedating and was more frequently associated with dry mouth than was risperidone. A 6-month study comparing quetiapine and risperidone reported better efficacy for risperidone (Potkin *et al.* 2006), with quetiapine associated with more polypharmacy. A 6-month double-blind comparative trial of quetiapine and olanzapine (Kinon *et al.* 2006) reported that quetiapine-treated patients were less likely to complete the study, although relapse rates were comparable overall in the two treatment groups. More weight gain occurred in olanzapine recipients. As yet, no studies have directly compared quetiapine with aripiprazole, iloperidone, asenapine, or lurasidone in the treatment of schizophrenia.

The most extensive comparative evaluation of quetiapine and other SGAs comes from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). In the Phase I study, more quetiapine-treated patients than olanzapine-treated patients had discontinued treatment by 18 months (78% vs. 64%), and a similar (not statistically significant) trend was seen in comparisons of quetiapine versus risperidone, ziprasidone, or perphenazine (Lieberman *et al.* 2005). In the Phase II study, discontinuation rates favored clozapine and olanzapine over risperidone and quetiapine (McEvoy *et al.* 2006). The results from the tolerability pathways were mixed and showed similar efficacy for quetiapine versus other agents (Stroup *et al.* 2007). The findings relating to quetiapine's relative adverse-effect profile in this formative study are presented in the section "Side Effects and Toxicology." Another interesting analysis from the CATIE schizophrenia studies (Stroup *et al.* 2007) examined how the patients originally assigned to the perphenazine arm of the Phase I study fared. In this analysis, switching to quetiapine was more efficacious than switching to any of the other agents. Many of the efficacy and tolerability differences between agents observed in the CATIE schizophrenia studies have been attributed to differential dosing profiles.

An analogous comparative trial of quetiapine, risperidone, and olanzapine was conducted with patients experiencing a first episode of psychosis: the Comparison of Atypicals in First Episode of Psychosis (CAFE) study. Here, discontinuation rates were similar across drugs over the 1-year trial (McEvoy *et al.* 2007). Another pragmatic trial in first-episode psychosis (Gomez-Revuelta *et al.* 2020) found a higher rate of all-cause drug discontinuation at 3-year follow-up with quetiapine (95%) in comparison with haloperidol (89%), ziprasidone (79%), aripiprazole (73%), risperidone (71%), and olanzapine (69%). Two studies inform the comparative efficacy and tolerability of quetiapine in adolescents with psychosis (and related conditions) (Arango *et al.* 2014; Perez-Iglesias *et al.* 2014). Perez-Iglesias *et al.* (2014) found that quetiapine increased weight and cholesterol levels over 3 months. Similarly, Arango *et al.* (2014) found that quetiapine increased weight (less so than olanzapine, more so than risperidone) over 6 months in children and adolescents, although in this study there was no rise in cholesterol in quetiapine-treated patients. A 12-week comparative trial of quetiapine XR versus aripiprazole in youths ages 12-17 years with first episode psychosis also found similar increases in weight and metabolic parameters that were more pronounced in the quetiapine-treated group (Jensen *et al.* 2019).

The use of quetiapine for patients with prodromal features of schizophrenia has not yet been studied. A small study of quetiapine for patients with schizophrenia and comorbid substance abuse was inconclusive (Brunette *et al.* 2009).

Mood Disorders

There is evidence that quetiapine is an effective and well-tolerated antipsychotic for treating patients with bipolar mania and bipolar depression (Keramatian *et al.* 2021). Bowden *et al.* (2005) demonstrated that quetiapine was superior to placebo in the treatment of mania. In this multicenter study, significantly more patients treated with quetiapine than with placebo met criteria for response (> 50% decrease from baseline score on the Young Mania Rating Scale) at 7, 21, and 84 days. Building on initial evidence for mood effects that was derived from observations on mood assessment items in the pivotal schizophrenia trials, the Quetiapine Experience with Safety and Tolerability (QUEST) study compared quetiapine with risperidone in a 4-month open-label, flexible-dose trial (Mullen *et al.* 2001). This study included patients with schizophrenia, schizoaffective disorder, bipolar disorder, and depression. At week 16, the mean dosage of quetiapine was 317 mg/day, and the mean dosage of risperidone was 4.5 mg/day. Mean improvement on the Hamilton Rating Scale for Depression was significantly greater in quetiapine recipients than in risperidone recipients.

Calabrese *et al.* (2005) and Thase *et al.* (2006) have studied quetiapine use for patients with bipolar depression. In an 8-week trial, Calabrese *et al.* (2005) compared two dosages of quetiapine (300 mg/day and 600 mg/day) with placebo. Both dosages were efficacious, with improvements observed across the full range of depressive and anxiety symptoms. Fifty-eight percent of patients met a priori criteria for treatment response. Additionally, this antidepressant effect was observed with a once-daily dosage regimen. In a subsequent similar study (Thase *et al.* 2006) of the same two dosages

(300 mg/day and 600 mg/day), quetiapine was again compared with placebo in an 8-week trial of patients with bipolar depression. Again, both dosages of quetiapine showed efficacy across a broad range of depressive symptoms. These two studies led to FDA approval of quetiapine for treating bipolar depression.

Two large 8-week international multicenter studies--Efficacy of Monotherapy Seroquel in BipOLar DEpressioN (EMBOLDEN) I (Young *et al.* 2010) and II (McElroy *et al.* 2010)--compared quetiapine 300 mg/day and 600 mg/day with lithium 600-1,800 mg/day and placebo (EMBOLDEN I) and with paroxetine 20 mg/day and placebo (EMBOLDEN II) for patients with bipolar disorder with a major depressive episode. In the first study (Young *et al.* 2010), quetiapine at both dosages, but not lithium, led to significant improvement in symptoms of depression and anxiety. Compared with patients receiving placebo, patients treated with quetiapine 300 mg/day and 600 mg/day showed significant improvement on the Sheehan Disability Scale. In the second study (McElroy *et al.* 2010), quetiapine 300 mg/day and 600 mg/day, but not paroxetine 20 mg/day, led to significant improvement in depressive and anxiety symptoms. Neither lithium nor paroxetine led to significant functional improvement over placebo in these studies. In both studies, a small subgroup of patients with rapid-cycling bipolar disorder did not improve significantly from baseline with any of the drugs administered (quetiapine, lithium, or paroxetine).

In a long-term naturalistic study (Ketter *et al.* 2010) of quetiapine administered to 96 patients with bipolar disorder in a clinical setting, 38.5% of patients continued taking quetiapine for 328 days without the addition of other psychotropics, whereas 22.9% continued taking quetiapine for 613 days with the addition of another psychotropic, most often for depression. In a small double-blind, placebo-controlled pilot study (DelBello *et al.* 2009) of quetiapine 300-600 mg/day for depressed adolescents with bipolar disorder, quetiapine neither differentiated from placebo nor induced a significant change in symptoms from baseline to endpoint on measures of depressive, anxiety, or manic symptoms or clinical global impressions of bipolar disorder severity. Bourin *et al.* (2014) reported superior efficacy when lithium was added to quetiapine XR, and this combination was well tolerated.

Doree *et al.* (2007) reported that in a pilot study (*n* = 20), quetiapine was an efficacious augmenting agent for antidepressant treatment in MDD. Anderson *et al.* (2009) also reported on quetiapine's efficacy as an adjunctive treatment for patients with refractory depression. Quetiapine XR monotherapy at a mean daily dosage of 162.2 mg was shown to decrease symptoms of MDD at 8 weeks when compared with placebo (Bortnick *et al.* 2011). Cutler *et al.* (2009) reported that quetiapine XR 300 mg/day led to significantly higher rates of response and remission when compared with placebo in MDD, whereas quetiapine XR 150 mg/day had a significant effect only on response when compared with placebo. Quetiapine at dosages of 150-300 mg/day is now approved by the FDA as an adjunct to antidepressant treatment for a major depressive episode. In one of the studies leading to FDA approval of quetiapine XR for this indication, El-Khalili *et al.* (2010) demonstrated that quetiapine XR at 300 mg/day led to significant improvement in symptoms of depression from the first week of treatment when compared with placebo. In a review of registration studies for the MDD indication, McIntyre *et al.* (2009) concluded that quetiapine XR provides rapid and sustained relief of MDD symptoms. Weisler *et al.* (2012) also reported substantial improvement in depressive symptoms in two 6-week clinical trials of quetiapine XR. Remission at 6 weeks was achieved by 23.5% of patients

taking 150 mg/day and by 28.8% of patients taking 300 mg/day of quetiapine. A review of extant published studies of quetiapine--and other SGAs--in treatment-resistant depression suggests that augmentation of antidepressants with quetiapine can be an effective therapy for such hard-to-treat patients (Cantu *et al.* 2021). The review also suggested that quetiapine might have particular benefit for patients with treatment-resistant depression that includes features of marked anxiety or marked insomnia. A retrospective analysis of controlled trials also suggested that quetiapine might be helpful in so-called melancholic depression (Peters *et al.* 2020). Lin *et al.* (2014) used a national insurance database from Taiwan to compare in a mirror image design the effect of augmentation of antidepressant therapy over 1 year for patients with MDD. Quetiapine, olanzapine, and aripiprazole augmentations were each effective in reducing health care utilization. Masi *et al.* (2015) reported improvement from and tolerability of quetiapine in a small open-label study comparing quetiapine and risperidone for adolescents with bipolar disorder and comorbid conduct disorder.

Anxiety Disorders

The sedative or calming effect of quetiapine was well described in a variety of product registration trials (Chengappa *et al.* 2003a; Weiden *et al.* 2006), and studies in bipolar I disorder and bipolar depression (Calabrese *et al.* 2005; Hirschfeld *et al.* 2006; Thase *et al.* 2006) demonstrated improvements in anxiety symptoms with quetiapine. A systematic review of quetiapine for comorbid anxiety symptoms in patients with mood disorders affirmed that quetiapine can be beneficial for these symptoms (Crapanzano *et al.* 2021).

In a small 8-week study (Vaishnavi *et al.* 2007) of social anxiety disorder treatment, there was no significant difference in Brief Social Phobia Scale scores between the quetiapine and placebo groups, although people who took quetiapine did show a robust response as measured by Clinical Global Impression-Improvement scale scores.

Two small studies of quetiapine augmentation for patients with generalized anxiety disorder (GAD) who had not responded to antidepressant therapy (Katzman *et al.* 2008; Simon *et al.* 2008) yielded contradictory results. A large double-blind, randomized, placebo-controlled study of monotherapy for GAD (Bandelow *et al.* 2010) compared quetiapine XR 50 mg/day or 150 mg/day, paroxetine 20 mg/day, and placebo. Significant separation from placebo on the primary outcome variable (mean reduction in Hamilton Anxiety Scale total score) was seen for quetiapine XR 50 mg/day and 150 mg/day as early as 4 days into treatment, but not for paroxetine. After 8 weeks of treatment, both quetiapine 150 mg/day and paroxetine 20 mg/day had higher anxiety remission rates (Hamilton Anxiety Scale score [?] 7) compared with placebo. Weight gain [?] 7% of body weight was noted in a higher percentage of patients treated with quetiapine than of those taking placebo. In a parallel-group, double-blind, placebo-controlled study by Katzman *et al.* (2011), 432 patients with GAD were randomly assigned to continue long-term treatment with quetiapine XR (50 mg/day, 150 mg/day, or 300 mg/day) or to switch to placebo after an open-label run-in and stabilization period. During the randomized treatment period (from the point of random assignment to the end of the study), quetiapine XR significantly increased the time to occurrence of an anxiety event and decreased anxiety symptoms compared with placebo.

An analysis comparing the tolerability of quetiapine XR (dosages of [?] 300 mg/day) versus placebo in patients with different disorders found significantly higher rates of discontinuation due to adverse effects (DAEs) among patients with GAD, bipolar depression, or refractory MDD than among patients with schizophrenia or mania (Wang *et al.* 2011). In a systematic review and meta-analysis of all available trials of SGA medications, quetiapine was observed to have the most robust effect on anxiety symptoms (LaLonde and Van Lieshout 2011). The antianxiety effects of quetiapine were observed at lower dosages (typically 150 mg/day) than those used in schizophrenia studies, and the effects included overall improvement as well as remission. However, quetiapine was also associated with weight gain and high rates of medication DAEs in these studies of anxiety disorder (LaLonde and Van Lieshout 2011). In three 8-week studies of quetiapine XR, Stein *et al.* (2011) reported DAE rates of 13%, 16%, and 24% for quetiapine dosages of 50 mg/day, 150 mg/day, and 300 mg/day, respectively. In an 8-week placebo-controlled comparative trial of quetiapine XR and escitalopram, comparable improvements in anxiety symptoms, occurring early in the study, were observed with quetiapine and escitalopram (Merideth *et al.* 2012). By contrast, in an 8-week trial in a more "real-world" population of patients with bipolar depression with substantial comorbidities (especially GAD), quetiapine XR showed no advantages over placebo (Gao *et al.* 2014).

At present, the FDA has not approved quetiapine for use in any anxiety disorder.

Other Disorders

Several small studies of quetiapine augmentation (at dosages up to 400 mg/day) of selective serotonin reuptake inhibitor pharmacotherapy in refractory OCD yielded contradictory results (Atmaca *et al.* 2002; Carey *et al.* 2005; Fineberg *et al.* 2005); although improvement in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores was noted in patients treated with quetiapine, the response to quetiapine did not differentiate from placebo. Quetiapine's efficacy as an augmenting agent with antidepressants in treatment-resistant OCD was recently reviewed in a meta-analysis of five double-blind randomized controlled trials (RCTs) (Komossa *et al.* 2010). Adjunctive quetiapine was not superior to placebo in reducing Y-BOCS scores by 25% (the criterion for response in these studies), but it did reduce the Y-BOCS scores more significantly by the endpoint compared with placebo. A small case series also showed that adjunctive quetiapine response may be enduring (Dell'Osso *et al.* 2006). Veale *et al.* (2014) conducted a meta-analysis of SGAs in OCD. In contrast to benefits seen with risperidone or aripiprazole, no effect was seen with augmentation with either quetiapine or olanzapine. A study of quetiapine augmentation for patients with refractory OCD showed comparable efficacy between quetiapine and aripiprazole over a 4-month treatment period (Talaei *et al.* 2020).

Quetiapine has been studied in the treatment of PTSD (Ahearn *et al.* 2006; Byers *et al.* 2010; Hamner *et al.* 2003; Kozaric-Kovacic and Pivac 2007; Sokolski *et al.* 2003; Stathis *et al.* 2005). All but one of the studies (Stathis *et al.* 2005) involved quetiapine being administered to veterans as an adjunctive agent added to selective serotonin reuptake inhibitors, other antidepressants, sedative-anxiolytics, or anticonvulsants. All were open-label studies, and with the exception of a retrospective chart review comparing quetiapine with the a_1 receptor antagonist prazosin (Byers *et al.* 2010), none had a comparison group. The average quetiapine dosage used in these studies was 100-335 mg/day administered for 6-8 weeks. Quetiapine decreased symptoms of avoidance, hyperarousal, and intrusive recollection in the populations studied.

Other Conditions and Patient Populations

Quetiapine has also been used for older adults. In a 1-year open-label trial of quetiapine treatment for 151 older adults (mean age 76.8 years) with psychotic disorders (McManus *et al.* 1999), 52% of patients showed symptom improvement (as measured by a 20% or greater decline in Brief Psychiatric Rating Scale total score). Seventy percent of patients had some organic condition, predominantly Alzheimer's disease, with the remaining patients having a diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder. Quetiapine was well tolerated at a mean dosage of 100 mg/day. A 10-week study comparing two dosages of quetiapine (100 mg/day and 200 mg/day) with placebo for nursing home residents with dementia and agitation (Zhong *et al.* 2007) reported that only the 200 mg/day quetiapine dosage was efficacious in treating agitation. Quetiapine (100 mg/day) was also compared with risperidone (1.0 mg/day), olanzapine (5.5 mg/day), and placebo over 36 weeks in the CATIE Alzheimer's disease study (Schneider *et al.* 2006). Overall, no effect on the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale score was seen with any of the agents, and there were no differences between agents in time to discontinuation.

In contrast to the encouraging findings from open-label studies of quetiapine for Parkinson's-associated psychosis, four of five later double-blind RCTs

(Kurlan *et al.* 2007; Ondo *et al.* 2005; Rabey *et al.* 2007; Shotbolt *et al.* 2009) found no benefit for quetiapine in this population. The single positive RCT (Fernandez *et al.* 2009) was small ($N = 16$) and excluded patients with delusions, which appear to be more difficult to treat than hallucinations in Parkinson's disease (Shotbolt *et al.* 2010). Another recent review of available clinical trials between 1991 and 2017 came to a similar conclusion that quetiapine's efficacy for psychosis in Parkinson's disease is not as favorable as originally thought (Chen *et al.* 2019).

Agitation is a core aspect of several conditions. Currier *et al.* (2006) reported an interesting study of quetiapine in agitated patients in the emergency department. Here, Currier and colleagues reported that quetiapine could be used as an acute antiagitation agent if the dosage titration was judicious. Postural hypotension was observed in this study. A study of quetiapine used to manage delirium for critical care patients showed prospectively that quetiapine did not induce QTc prolongation in this potentially at-risk population (Lee *et al.* 2019). Other studies of quetiapine and agitation report benefits in treating hostility both for adults with schizophrenia (Chengappa *et al.* 2003a) or bipolar disorder (Buckley *et al.* 2007) and for children with hostile behaviors (Barzman *et al.* 2006; Findling *et al.* 2007).

Black *et al.* (2014) examined low-dosage quetiapine (150 mg/day) and moderate-dosage quetiapine (300 mg/day) versus placebo in an 8-week, double-blind trial of inpatients with borderline personality disorder. Both dosages of quetiapine were effective across a range of symptoms for these patients, although there were more side effects with moderate-dosage quetiapine.

Side Effects and Toxicology

To illustrate the profile of adverse effects typically seen with quetiapine, we have tabulated the results from an 8-week RCT (Zhong *et al.* 2006) (Table 28-1) in which quetiapine was compared with risperidone. Overall, quetiapine was well tolerated, with only 6% of patients discontinuing treatment because of adverse effects.

TABLE 28-1. Comparative side-effect profile of quetiapine versus risperidone: adverse effects present in [?] 5% of patients in an 8-week study

Adverse effect	Quetiapine (*n* = 338; median dosage 525 mg/day), *n* (%)	Risperidone (*n* = 334; median dosage 5.2 mg/day), *n* (%)	*P* value*
Somnolence	89 (26.3)	66 (19.7)	0.044
Headache	51 (15.1)	56 (16.7)	0.599
Weight gain	48 (14.2)	45 (13.4)	0.824
Dizziness	48 (14.2)	32 (9.6)	0.0737
Dry mouth	41 (12.1)	17 (5.1)	< 0.01
Dyspepsia	22 (6.5)	26 (7.8)	0.552
Nausea	21 (6.2)	22 (6.6)	0.876
Pain	21 (6.2)	24 (7.2)	0.536
Asthenia	17 (5.0)	14 (4.2)	0.714
Agitation	17 (5.0)	10 (3.0)	0.238
Pharyngitis	15 (4.4)	24 (7.2)	0.140
Akathisia	13 (3.8)	28 (8.4)	0.016
Vomiting	13 (3.8)	18 (5.4)	0.364
Dystonia	1 (0.3)	18 (5.4)	< 0.001

*Fisher exact test, unadjusted.

Source. Adapted from Zhong *et al.* 2006.

On average, the adverse-effect profile of the XR formulation of quetiapine is similar to that of the IR formulation.

Somnolence, Sedation, and Dizziness

Somnolence is a common side effect of quetiapine that probably relates to its antihistaminergic activity. Although somnolence occurs early in treatment and generally decreases over time, it may persist in some patients. It may also cause patients to stop taking their medication, because sedation is generally a poorly tolerated side effect. In the bipolar depression study by Calabrese *et al.* (2005), somnolence was observed in 24% of patients taking quetiapine at a dosage of 300 mg/day and in 27% of patients taking 600 mg/day. In the long-term study by Ketter *et al.* (2010), sedation was present in 19.8% of patients. Dizziness is another troublesome side effect, and it may be associated with postural hypotension, an effect that is of even greater concern. As with sedation, dizziness can sometimes cause discontinuation of quetiapine therapy. A thoughtful review (Modesto-Lowe *et al.* 2021) of quetiapine's sedative effect evaluated the data on off-label use of quetiapine for insomnia.

Metabolic Effects

There is major concern about antipsychotic-induced weight gain and metabolic disturbances (Allison *et al.* 1999; Newcomer 2005; Newcomer *et al.* 2002). Quetiapine is clearly associated with weight gain, although the weight gain effect is not as great as

that seen with clozapine or olanzapine. On the other hand, the weight gain effect of quetiapine is greater than that of ziprasidone or aripiprazole (Newcomer 2005) and that of the newer agents asenapine (Allergan 2021) and lurasidone (Sunovion 2022).

In an 8-week comparative study by Zhong *et al.* (2006), weight gain that was clinically significant (a 7% increase above baseline weight) was observed in 10.4% of patients taking quetiapine and in 10.5% of patients taking risperidone. In the Phase I CATIE study, quetiapine had a moderate effect on weight (and other aspects of the metabolic profile) compared with other agents (Lieberman *et al.* 2005). Those data are shown in Table 28-2. In the first-episode CAFE study, quetiapine had a less favorable weight-effects profile than olanzapine or risperidone. Eighty percent of patients taking quetiapine gained weight, compared with 50% of those taking olanzapine and 2% of those taking risperidone. Interestingly, female patients taking quetiapine were less likely than male patients to gain weight in this 1-year study of patients treated for their first episode of psychosis (Patel *et al.* 2009). It is also important to consider quetiapine's propensity to induce weight gain among patients with bipolar disorder (especially because these patients may also be taking lithium or valproic acid). In the 8-week EMBOLDEN I (Young *et al.* 2010) and

EMBOLDEN II (McElroy *et al.* 2010) studies, weight gain of more than 7% of baseline weight was present in 4.6% and 9%, respectively, of patients taking quetiapine 300 mg/day, compared with 8.3% and 11.3%, respectively, of those taking quetiapine 600 mg/day. In EMBOLDEN I and EMBOLDEN II, the average weight gains in quetiapine-treated patients were 0.6 kg and 1.1 kg, respectively, for the 300 mg/day groups and 0.8 kg and 1.7 kg, respectively, for the 600 mg/day groups. A recent review of adverse effects of several SGAs in more pragmatic trials suggested a more complex assessment of risk, with mixed results for quetiapine with respect to the development of diabetes and dyslipidemia (Bernardo *et al.* 2021), although the rigor of the studies included limits the generalizability of findings.

TABLE 28-2. Comparative metabolic profiles of antipsychotics in the Phase I CATIE schizophrenia trial: change from baseline

	Olanzapine	**Quetiapine**	**Perphenazine**	**Risperidone**	**Ziprasidone**	***P* value**
Weight gain > 7%, *n*/total *N* (%)	92/307 (30)	49/305 (16)	29/243 (12)	42/300 (14)	12/161 (7)	< 0.001
Weight change (lb), mean +- SE	9.4 +- 0.9	1.1 +- 0.9	2.0 +- 1.10	0.8 +- 0.9	[?] 1.6 +- 1.10	< 0.001
Blood glucose change (mg/dL), exposure-	13.7 +- 2.50	7.5 +- 2.5	5.4 +- 2.8	6.6 +- 2.5	2.9 +- 3.4	0.59

Note. *P* values for laboratory values and for the change in weight are based on ranked analysis of covariance with adjustment for whether patients had an exacerbation in the preceding 3 months and the duration of exposure to the study drug in Phase I. Mean values for metabolic factors (other than weight change) were also adjusted for duration of exposure to the study drug.

SE = standard error.

Source. Adapted from Table 3 (p. 1220) in Lieberman *et al.* 2005.

	Olanzapine	**Quetiapine**	**Perphenazine**	**Risperidone**	**Ziprasidone**	***P* value**
adjusted mean +- SE						
Glycosylated hemoglobin change (%), exposure-adjusted mean +- SE	0.40 +- 0.07	0.04 +- 0.08	0.09 +- 0.09	0.07 +- 0.08	0.11 +- 0.09	0.01
Cholesterol change (mg/dL), exposure-adjusted mean +- SE	9.4 +- 2.4	6.6 +- 2.4	1.5 +- 2.7	[?] 1.3 +- 2.40	[?] 8.2 +- 3.20	< 0.001
Triglycerides change (mg/dL), exposure-adjusted mean +- SE	40.5 +- 8.90	21.2 +- 9.20	9.2 +- 10.1	[?] 2.4 +- 9.10	[?] 16.5 +- 12.20	< 0.001

Note. P values for laboratory values and for the change in weight are based on ranked analysis of covariance with adjustment for whether patients had an exacerbation in the preceding 3 months and the duration of exposure to the study drug in Phase I. Mean values for metabolic factors (other than weight change) were also adjusted for duration of exposure to the study drug.

SE = standard error.

Source. Adapted from Table 3 (p. 1220) in Lieberman *et al.* 2005.

In the bipolar depression study by Calabrese *et al.* (2005), the mean increases in glucose levels were 6 mg/dL and 3 mg/dL with quetiapine dosages of 600 mg/day and 300 mg/day, respectively. In the comparative study of quetiapine and risperidone in the treatment of schizophrenia (Zhong *et al.* 2006), the mean increases from baseline in fasting glucose levels were 1.8 mg/dL with quetiapine and 5.6 mg/dL with risperidone. The metabolic profile of quetiapine appeared moderate in the Phase I CATIE schizophrenia study (see Table 28-2. Newcomer *et al.* (2009) conducted a euglycemic clamp study of quetiapine and found little evidence of insulin insensitivity. A recent meta-analysis by the Cochrane group involving head-to-head comparisons of SGAs (Komossa *et al.* 2010) found that quetiapine was associated with significantly greater cholesterol elevations than risperidone (mean difference 8.61 mg/dL) and ziprasidone (mean difference 16.01 mg/dL). In the CATIE Phase I trial (Lieberman *et al.* 2005), which included patients with chronic schizophrenia, quetiapine led to a mean change from baseline fasting triglyceride levels of + 19.2 mg/dL, whereas a mean change of + 42.9 mg/dL was observed for olanzapine, + 8.3 mg/dL for perphenazine, [?] 2.6 mg/dL for risperidone, and [?] 18.1 mg/dL for ziprasidone. In a population of young patients with early psychosis treated with quetiapine, olanzapine, or risperidone, the CAFE study (Patel *et al.* 2009) found that elevations in fasting triglyceride levels at 52 weeks were significantly greater in quetiapine-treated patients than in risperidone-treated patients (44.3 vs. 8.2 ng/mL, respectively). Correll *et al.* (2014) reported baseline results from the pragmatic study Recovery After an Initial Schizophrenia

Episode. All patients were in their first episode of psychosis, with less than 6 months of exposure to antipsychotics. Use of quetiapine was associated with a high ratio of triglycerides to high-density lipoprotein cholesterol. The extent to which patients transition during treatment from a normative metabolic state to dysregulation is also informative. In the first-episode CAFE study, treatment-emergent metabolic syndrome was observed among 51 patients (13.4% of the population in a study where 4.3% met metabolic syndrome criteria at study onset), with a distribution of 22 patients taking olanzapine, 18 taking quetiapine, and 11 taking risperidone (Patel *et al.* 2009). Another recent study of antipsychotic use by adolescents found an elevated risk of type 2 diabetes mellitus, with longer duration of antipsychotic exposure and olanzapine use each conferring greater risk (Correll *et al.* 2014). In another first-episode comparative study, Perez-Iglesias *et al.* (2014) found that patients with first-episode psychosis treated with quetiapine, aripiprazole, or ziprasidone gained weight over 12 weeks of treatment, with a greater than 7% weight increase noted for 32% of patients receiving quetiapine, 45% of those receiving aripiprazole, and 23% of those receiving ziprasidone. Quetiapine and aripiprazole were also associated with greater increases in total cholesterol and low-density lipoprotein cholesterol. Overall, quetiapine appears to carry a risk of causing weight gain and other metabolic disturbances. The potential that quetiapine may preferentially raise triglycerides is noteworthy, given that this effect could be a harbinger for later insulin resistance. This observation merits further consideration and vigilance over time.

Quetiapine is associated with a low risk of raising prolactin levels (Hamner *et al.* 1996; Lieberman *et al.* 2005; Small *et al.* 1997; Zhong *et al.* 2006).

Extrapyramidal Side Effects

The low-EPS advantage of quetiapine is compelling and consistent across studies. In the Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication switch study (Larmo *et al.* 2005), switching to quetiapine from haloperidol, olanzapine, or risperidone was associated with a robust reduction in EPS. This low propensity for EPS was also seen in the bipolar depression studies (Calabrese *et al.* 2005; Thase *et al.* 2006).

Cardiovascular Effects

Quetiapine's prescribing information (AstraZeneca 2013, 2020) carries a boxed warning similar to that required in the prescribing information of many other antipsychotics concerning cardiovascular risks. However, the CATIE trial found no evidence of a heightened QTc risk with quetiapine relative to other SGAs and perphenazine (Lieberman *et al.* 2005).

Other Effects

The potential of quetiapine to induce cataracts was studied in a pragmatic follow-up trial of patients (N = 37; mean age 23 years) with first-episode psychosis that included regular slit-lamp ophthalmological examinations (Whitehorn *et al.* 2004). After exposure to quetiapine 500-600 mg/day for a mean of 22.4 months, none of the patients developed any ocular changes. Most clinicians do not obtain specialist eye examinations when prescribing quetiapine.

Abnormalities in thyroid hormone levels were observed in the large premarketing trials of quetiapine (Arvanitis and Miller 1997). A small RCT did find lower total thyroid hormone levels with quetiapine use but no significant changes in free thyroxine or thyroid-stimulating hormone levels (Kelly and Conley 2005). Constipation, abdominal pain, and hypotension have also been associated with quetiapine use (AstraZeneca 2013).

A curious and unsubstantiated claim is that quetiapine might have abuse potential (Pierre *et al.* 2005; Pinta and Taylor 2007). This observation merits further consideration and vigilance.

Use During Pregnancy

As is the case with all SGAs, there is little information about the effects of quetiapine during pregnancy. A prospective study by McKenna *et al.* (2005) examined a sample of pregnant women in Canada, Israel, and England treated with SGAs, which was matched to a comparison group of pregnant women who were not exposed to these agents. Among them were 36 women treated with quetiapine. The pregnancy outcomes in the exposed and comparison groups were not significantly different, with the exceptions of the rate of low birth weight, which was 10% in exposed babies and 2% in the comparison group ($P = 0.05$), and the rate of therapeutic abortions, which was 9.9% in exposed women and 1.3% in the comparison group ($P = 0.003$). These findings suggest that atypical antipsychotics as a group are not associated with an increased risk for major malformations. Cohen *et al.* (2018) reported data from a national pregnancy registry for atypical antipsychotics and found no evidence for heightened risk of major malformations after first trimester exposure to quetiapine.

Conclusion

Quetiapine is now a well-established and widely prescribed antipsychotic. As detailed earlier, there is strong evidence for its efficacy in all of the current FDA-approved indications. Quetiapine is also used extensively under circumstances not approved by the FDA (i.e., off-label use), and evidence for its efficacy in some of these uses has been reviewed in this chapter. Additional clinical trials of quetiapine are ongoing (www.clinicaltrials.gov).

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CHAPTER 29

Risperidone and Paliperidone

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Risperidone and paliperidone are atypical antipsychotics frequently used in the treatment of primary psychotic disorders, as well as in the treatment of a variety of other psychiatric conditions, including affective, compulsive, and neurodevelopmental disorders. In this chapter, we describe the molecular and pharmacological properties of these two related compounds and review the evidence supporting their use in the treatment of psychiatric disorders.

History and Discovery

A decade before clozapine was approved for marketing in the United States, Janssen Pharmaceuticals established a program to examine the potential role of serotonergic agents in schizophrenia. Early interest in serotonergic agents stemmed from preclinical literature demonstrating that both behavioral effects of dopamine receptor agonists and haloperidol-induced catalepsy could be modulated by serotonin$_2$ (5-HT$_2$) receptor antagonists; in addition, the early butyrophenone derivative pipamperone, which was observed to reduce agitation and improve social activity for patients with severe depression, was found to possess primarily 5-HT_2 receptor antagonist activity (Ansoms *et al.* 1977; Leysen *et al.* 1978).

In 1981, Janssen Pharmaceuticals developed setoperone, a 5-HT_2 receptor antagonist with weak $dopamine_2$ (D_2) receptor antagonism that displayed antipsychotic effects and efficacy for negative symptoms in a preliminary open trial (Ceulemans *et al.* 1985). Janssen Pharmaceuticals additionally synthesized a selective 5-HT_{2A} and 5-HT_{2C} receptor antagonist, ritanserin, which was shown to decrease extrapyramidal side effects

(EPS) when combined with haloperidol in at studies. Ritanserin also was active in animal models of anxiety (Colpaert *et al.* 1985; Meert and Colpaert 1986) and partially ameliorated the behavioral effects of lysergic acid diethylamide (LSD) (Colpaert *et al.* 1985). In placebo-controlled trials of patients with chronic schizophrenia, addition of ritanserin to first-generation antipsychotics (FGAs) reduced negative symptoms and EPS (Bersani *et al.* 1990; Duinkerke *et al.* 1993; Gelders 1989; Reyntjens *et al.* 1986). Concluding that 5-HT_2 receptor antagonism might increase the effectiveness of D_2 blockers, particularly for negative symptoms, and reduce EPS, but that it was not sufficiently effective as monotherapy, Paul Janssen and colleagues undertook development of risperidone, which combined potent 5-HT_{2A} and D_2 receptor blockade.

After extensive preclinical characterization (Janssen *et al.* 1988), risperidone was first studied in clinical trials in 1986 and received FDA approval for marketing in the United States in 1994. By the time risperidone became available to clinicians, the prominence of theories citing 5-HT_2 enhancement of D_2 receptor antagonism as a primary mechanism for clozapine's atypical properties (Meltzer *et al.* 1989), as well as the evidence from registration trials of reduced EPS and greater efficacy compared with high-dose haloperidol, resulted in enthusiasm for the first of the "serotonin dopamine antagonists." Risperidone was rapidly incorporated into clinical practice in the United States, where within 2 years it became the most frequently prescribed antipsychotic agent. In 2003, risperidone microspheres (Consta) received FDA approval as the first long-acting second-generation antipsychotic (SGA) designed for intramuscular injection. In December 2006, Janssen Pharmaceuticals introduced paliperidone (9-hydroxyrisperidone), the active metabolite of risperidone, formulated as an extended-release tablet marketed under the brand name Invega. Extended-release paliperidone is approved for the treatment of schizophrenia and schizoaffective disorder. A long-acting depot preparation, paliperidone palmitate (Sustenna), received FDA approval for schizophrenia in 2009 and for schizoaffective disorder in 2014; it was the first once-monthly depot formulation of an SGA to become available in the United States. In May 2015, a new formulation of paliperidone with a 3-month injection interval, paliperidone palmitate 3-month formulation (PP3M; Invega Trinza), was approved by the FDA for the treatment of schizophrenia under its priority review process. This formulation's 3-month schedule provides the longest dosing interval available for patients with schizophrenia.

Structure-Activity Relations and Pharmacological Profile

Risperidone, or 3-[2-(4-[6-fluoro-1,2-benzisoxazol-3-yl]-1-piperidinyl)ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, is a benzisoxazole derivative characterized by very high affinity for 5-HT$_{2A}$ receptors and moderately high affinity for D$_2$, histamine 1 (H$_1$), and a$_1$- and a$_2$-adrenergic receptors (Figure 29-1). In vitro, the affinity of risperidone for 5-HT$_{2A}$ receptors is roughly 10 to 20 times greater than that for D$_2$ receptors (Leysen *et al.* 1994; Schotte *et al.* 1996); in vivo binding to rat striatal D$_2$ receptors occurs at a dosage 10 times higher than does binding to 5-HT$_{2A}$ receptors (Leysen *et al.* 1994). The affinity for 5-HT$_{2A}$ receptors is more than 100 times greater than for other serotonin receptor subtypes.

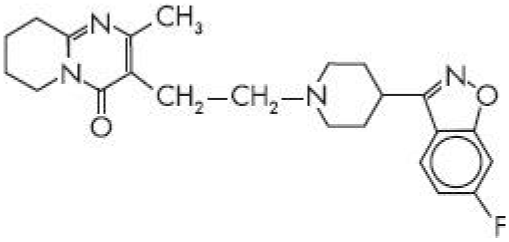

FIGURE 29-1. Chemical structure of risperidone.

Risperidone's active metabolite 9-hydroxyrisperidone (paliperidone) (Figure 29-2) has a similar receptor affinity profile, although paliperidone has lower affinity for a_1- and a_2-adrenergic receptors. Both risperidone and paliperidone display a high affinity for 5-HT_{2A} receptors in rat brain tissue and for cloned human receptors expressed in COS-7 cells (Leysen *et al.* 1994). Risperidone binds to 5-HT_{2A} receptors with approximately 20 times greater affinity compared with clozapine and 170 times greater affinity compared with haloperidol (Leysen *et al.* 1994).

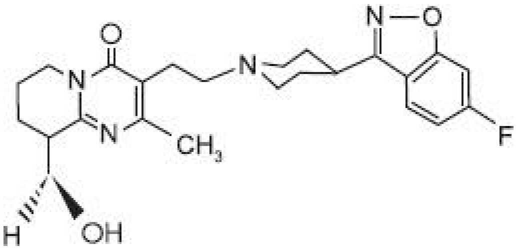

FIGURE 29-2. Chemical structure of paliperidone.

The affinity of risperidone for D_2 receptors is approximately 50 times greater than that of clozapine and approximately 20%-50% that of haloperidol (Leysen *et al.* 1994) (Table 29-1). Binding affinity for D_2 receptors was similar in rat mesolimbic and striatal tissue and in the long and short forms of cloned human D_2 receptors expressed in embryonic kidney cells (Leysen *et al.* 1993a). The affinities of risperidone and paliperidone for dopamine$_4$ (D_4) and dopamine$_1$ (D_1) receptors are similar to those of clozapine and haloperidol (Leysen *et al.* 1994). Risperidone and paliperidone have essentially no affinity for muscarinic acetylcholine receptors and modest H_1 receptor activity. Unlike haloperidol, risperidone does not bind to sigma sites (Leysen *et al.* 1994). However, compared with other agents, including paliperidone, risperidone has a high affinity for a_2-adrenergic receptors that is substantially greater than that of clozapine or any FGA and that approaches the affinity of phentolamine (Richelson 1996). The affinity of risperidone for a_1-adrenergic receptors is roughly comparable to that of chlorpromazine and approximately 5-10 times greater than that of clozapine (Leysen *et al.* 1993b; Richelson 1996). The median effective dose of risperidone needed to inhibit D_2-mediated apomorphine-induced stereotypies in rats is 0.5 mg/kg; at this dosage, approximately 40% of D_2 receptors are occupied, as are 80% of 5-HT_{2A} receptors, 50% of H_1 receptors, 38% of a_1-adrenergic receptors, and 10% of a_2-adrenergic receptors (Leysen *et al.* 1994).

TABLE 29-1. Receptor-binding affinities (K_i values, in nM) of representative antipsychotics in cloned human receptors and rat brain

	Paliperidone	**Risperidone**	**Haloperidol**	**Clozapine**
Dopaminergic				
D_2*	4.8	5.9	2.2	190
D_1*	670	620	270	540
Serotonergic				
5-HT_{2A}*	1.0	0.52	200	9.6
5-HT_{1A}*	590	420	1,500	140
Adrenergic				
a_1^+	4.0	2.3	19	23

*Cloned human receptor.

$^+$Rat brain.

Source. Adapted from Schotte *et al.* 1996.

	Paliperidone	**Risperidone**	**Haloperidol**	**Clozapine**
a_2^+	17	7.5	> 5,000	160
H_1 histaminergic*	32	27	790	0 .23
Muscarinic$^+$	3,570	> 5,000	4,670	34

*Cloned human receptor.

$^+$Rat brain.

Source. Adapted from Schotte *et al.* 1996.

Several groups have studied the occupancy of D_2 and 5-HT_2 receptors in patients with schizophrenia, using PET or SPECT ligand-binding techniques. Kapur *et al.* (1999) used PET to measure D_2 occupancy with ^{11}C-labeled raclopride and 5-HT_2 occupancy with ^{18}F-labeled setoperone in patients with chronic schizophrenia maintained on a stable clinician-determined dosage of risperidone. The PET was performed 12-14 hours after the last dose of risperidone. Occupancy of D_2 receptors ranged from 63% to 89%; 50% occupancy was calculated to occur with a daily risperidone dosage of 0.8 mg. Similar ranges have been found with paliperidone dosages between 3 and 15 mg/day, with 50% occupancy occurring at approximately 2.5 mg/day (Arakawa *et al.* 2008). Patients treated with risperidone (6 mg/day) exhibited a mean D_2 occupancy of 79%, which was consistent with the mean occupancy of 82% previously reported by Nyberg *et al.* (1999) and would be expected to exceed the putative threshold for EPS for some patients. A similar degree of D_2 occupancy was calculated to occur with olanzapine at approximately 30 mg/day (Kapur *et al.* 1999). A maximal 5-HT_2 occupancy of greater than 95% was achieved with risperidone at daily dosages as low as 2-4 mg. In a small sample of patients treated biweekly for at least 10 weeks with risperidone microspheres (Consta), Remington *et al.* (2006) found that the 25 mg dose produced a mean D_2 occupancy of 54% (preinjection) and 71% (postinjection), whereas the 50-mg dose produced occupancy levels of 65% (preinjection) and 74% (postinjection). Arakawa *et al.* (2008) found a D_2 occupancy of 58% with paliperidone at 3 mg/day and 77% with 9 mg/day, consistent with clinical estimates that paliperidone is roughly half as potent as risperidone, perhaps because of reduced bioavailability (de Leon *et al.* 2010).

Preclinical characterization of risperidone in rats revealed more potent antiserotonergic activity compared with ritanserin in all tests (Janssen *et al.* 1988). For example, in reversal of tryptophan-induced effects in rats, risperidone was 6.4 times more potent than ritanserin for reversal of peripheral 5-HT$_2$-mediated effects and 2.4 times more potent for reversal of centrally mediated 5-HT$_2$ effects (Janssen *et al.* 1988). Risperidone was also found to completely block discrimination of LSD, in contrast to the partial attenuation observed with ritanserin (Meert *et al.* 1989). Although risperidone demonstrated activity in all dopamine-mediated tests, the dose-response pattern differed from that of haloperidol (Janssen *et al.* 1988). The two drugs were roughly equipotent for inhibition of certain dopamine effects, such as amphetamine-induced oxygen hyperconsumption, whereas the dosage of risperidone necessary to cause pronounced catalepsy in rats was 18 times higher than that of haloperidol (Janssen *et al.* 1988). Risperidone depressed vertical and horizontal activity in rats at a dosage 2-3 times greater than that of haloperidol but required dosages more than 30 times greater than those of haloperidol to depress small motor movements (Megens *et al.* 1988).

Pharmacokinetics and Disposition

Risperidone is rapidly absorbed after oral administration, with peak plasma levels achieved within 1 hour (Heykants *et al.* 1994). In early Phase I studies, risperidone demonstrated linear pharmacokinetics at dosages between 0.5 and 25 mg/day (Mesotten *et al.* 1989; Roose *et al.* 1988).

After a single dose of the extended-release formulation of paliperidone (Invega), serum concentrations gradually increase until a maximum concentration is achieved approximately 24 hours after ingestion. Absorption of paliperidone is approximately 50% greater when taken with a meal compared with the fasting state. Extended-release paliperidone also demonstrates dose-proportional pharmacokinetics within the recommended dosing range (3-12 mg/day).

Because risperidone lacks a hydroxyl group to which an ester can be bound for a traditional oil-based depot preparation, polymer microsphere technology was used to produce a slow-release injectable formulation. Risperidone microspheres do not begin to release appreciable amounts of drug until 3 weeks after injection and continue to release drug for approximately 4 weeks, with maximal drug release occurring about 5 weeks after injection.

Paliperidone palmitate is an esterified form of paliperidone and is poorly soluble in water. It dissolves slowly after intramuscular injection, after which it is hydrolyzed to active paliperidone and absorbed into the systemic circulation. Systemic availability of paliperidone begins on day 1 and can last as long as 126 days after injection. Maximum blood levels are achieved a median of 13 days after injection. A dosage of 117 mg/month is recommended by the manufacturer; a study from the United Kingdom revealed a mean dosage in clinical practice of approximately 110 mg/month (Deslandes *et al.* 2018). Intramuscular injection in the deltoid produces blood levels ~ 28% higher than those produced with gluteal injection. The 3-month formulation of paliperidone palmitate has an extended apparent elimination half-life that permits this longer dosing interval. Risperidone is 90% plasma protein bound, whereas paliperidone is 74% plasma protein bound (Borison *et al.* 1994). The absolute bioavailability of risperidone is about 100%; that of extended-release paliperidone is about 28%. Paliperidone may achieve lower concentrations in the brain because of its higher affinity for the extruding P-glycoprotein transporter, which limits the amount of drug crossing the blood-brain barrier (de Leon *et al.* 2010).

Risperidone is metabolized by hydroxylation of the tetrahydro-pyrido-pyrimidinone ring at the seven and nine positions and by oxidative *N*-dealkylation (Mannens *et al.* 1993). The most important metabolite, 9-hydroxyrisperidone (paliperidone), accounts for up to 31% of the dose excreted in the urine. Because hydroxylation of risperidone is catalyzed by cytochrome P450 (CYP) 2D6, the half-life of the parent compound varies according to the relative activity of this enzyme. In extensive metabolizers, which include about 90% of white individuals and as many as 99% of Asian individuals, the half-life of risperidone is approximately 3 hours. Approximately 60% of paliperidone is excreted unchanged in the urine, and the remainder is metabolized by at least four different pathways (dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission), none of which accounts for more than 10% of the total. The terminal half-life of 9-hydroxyrisperidone (and of extended-release paliperidone) is 23 hours. Poor metabolizers metabolize risperidone primarily via oxidative pathways; the half-life may exceed 20 hours. In extensive metabolizers, radioactivity from ^{14}C-labeled risperidone is not detectable in plasma 24 hours after a single dose, whereas 9-hydroxyrisperidone accounts for 70%-80% of radioactivity. In poor metabolizers, risperidone is primarily responsible for radioactivity after 24 hours. In the U.S. multicenter registration trial, the correlations between risperidone dose and serum risperidone and 9-hydroxyrisperidone concentrations were 0.59 and 0.88, respectively (Anderson *et al.* 1993). Because of paliperidone's longer half-life, its serum concentrations at steady state are approximately 5 to 10 times higher than risperidone concentrations in CYP2D6 extensive metabolizers treated with risperidone (de Leon *et al.* 2010). However, in CYP2D6 poor metabolizers and patients concurrently taking CYP2D6 inhibitors, risperidone concentrations increase progressively according to reduced CYP2D6 activity (Kneller *et al.* 2020). The ratio of risperidone to paliperidone concentration is typically more than four times higher in poor metabolizers than in extensive metabolizers (Zhang *et al.* 2020).

Mechanism of Action

As previously discussed, risperidone was developed specifically to exploit the apparent pharmacological advantages of combining 5-HT$_2$ receptor antagonism with D$_2$ receptor blockade. Selective 5-HT$_{2A}$ receptor antagonists administered alone have demonstrated activity in several animal models suggestive of antipsychotic effect, including blockade of both amphetamine-and phencyclidine (PCP)-induced locomotor activity

(Schmidt *et al.* 1995). Dizocilpine-induced disruption of prepulse inhibition is also blocked by 5-HT$_{2A}$ receptor antagonists, suggesting that sensory gating deficits characteristic of schizophrenia and perhaps resulting from glutamatergic dysregulation might also benefit from the 5-HT$_2$ receptor antagonism of risperidone (Varty *et al.* 1999). The disruption of prepulse inhibition by dizocilpine (MK-801, a noncompetitive *N*-methyl-D-aspartate [NMDA] receptor antagonist) is attenuated by SGAs but not by first-generation D$_2$ receptor blockers (Geyer *et al.* 1990). From a study in which the selective 5-HT$_{2A}$ receptor antagonist M100907 was added to low-dose raclopride (a selective D$_2$ receptor blocker), Wadenberg *et al.* (1998) concluded that 5-HT$_{2A}$ antagonism facilitates D$_2$ receptor antagonist blockade of conditioned avoidance, another behavioral model associated with antipsychotic efficacy, but does not block conditioned avoidance when administered alone.

One mechanism by which risperidone, paliperidone, and similar atypical agents might increase efficacy for negative symptoms and cognitive deficits and reduce risk for EPS is via 5-HT$_{2A}$ receptor modulation of dopamine neuronal firing and cortical dopamine release. Prefrontal dopaminergic hypoactivity has been postulated to underlie negative symptoms and cognitive deficits in schizophrenia (Goff and Evins 1998); both clozapine and ritanserin have been shown to increase dopamine release in the prefrontal cortex, whereas haloperidol does not (Busatto and Kerwin 1997). After 21 days of administration, risperidone, but not haloperidol, continued to increase dopamine turnover in the dorsal striatum and prefrontal cortex (Stathis *et al.* 1996). Ritanserin has been shown to increase midbrain dopamine cell firing by blocking a tonic inhibitory serotonin input (Ugedo *et al.* 1989). Ritanserin also normalized ventral tegmental dopamine neuron firing patterns in rats after hypofrontality was induced by experimental cooling of the frontal cortex (Svensson *et al.* 1989).

Svensson *et al.* (1995) performed a series of elegant studies examining the impact of atypical antipsychotics on ventral tegmental dopamine firing patterns disrupted by glutamatergic NMDA receptor antagonists. In healthy human subjects, administration of the NMDA antagonist ketamine is widely regarded as a promising model for the development of several clinical aspects of schizophrenia, including psychosis, negative symptoms, and cognitive deficits (Goff and Coyle 2001; Krystal *et al.* 1994). In rats, administration of the NMDA channel blocker dizocilpine or PCP increased burst firing of ventral tegmental dopamine neurons predominantly projecting to limbic structures but reduced firing of mesocortical tract dopamine neurons and disrupted firing patterns. Administration of ritanserin or clozapine preferentially increased firing of dopamine neurons with cortical projections, and when added to a D_2 blocker, ritanserin increased dopamine release in prefrontal cortex. In addition to modulating ventral tegmental dopamine neuron firing, risperidone blocks 5-HT_2 receptors on inhibitory GABAergic interneurons, which could also influence activity of cortical pyramidal neurons that are regulated by these local inhibitory circuits (Gellman and Aghajanian 1994).

In placebo-controlled clinical trials, 5-HT_2 receptor antagonists have shown efficacy in reducing antipsychotic-induced parkinsonism and akathisia (Duinkerke *et al.* 1993; Poyurovsky *et al.* 1999). This effect may reflect 5-HT_{2A} antagonist effects on nigrostriatal dopamine release. When combined with haloperidol, selective 5-HT_2 receptor antagonists increase dopamine metabolism in the striatum and prevent an increase in D_2 receptor density, thereby possibly reducing the effects of D_2 receptor blockade and dopamine supersensitivity (Saller *et al.* 1990). These agents do not affect dopamine metabolism in the absence of D_2 blockade.

The relative importance of 5-HT_2 receptor antagonist activity in producing atypical characteristics is the subject of debate. Most SGAs (with the exception of partial D_2 agonists) have dissociation constants for the D_2 receptor that are larger than the dissociation constant of dopamine (Carboni *et al.* 2012; Kapur and Seeman 2001; Seeman 2002). This "loose binding" to the D_2 receptor may allow displacement by endogenous dopamine and may reduce the risks of EPS and hyperprolactinemia. Risperidone and paliperidone are "tightly bound" to the D_2 receptor, with a dissociation constant smaller than that of dopamine (Kozielska *et al.* 2012; Seeman

2002). A model for atypical antipsychotic mechanisms that emphasizes D_2 dissociation constants would predict that the apparent atypicality of risperidone, compared with that of haloperidol, reflects the reduced D_2 receptor occupancy achieved by more favorable dosing rather than the intrinsic pharmacological characteristics of risperidone. According to some binding data, a comparable clinical dosage of haloperidol would be approximately 4 mg/day, rather than 20 mg/day as used in the North American multicenter registration trial (Kapur *et al.* 1999). Consistent with this view, benefits of risperidone for negative symptoms and EPS were less apparent when compared with lower dosages of haloperidol or with lower-potency FGAs (see "Indications and Efficacy" section later in this chapter) than when compared with high-dose haloperidol (20 mg/day).

An additional mechanism that may possibly contribute to the increased efficacy of risperidone and paliperidone is their a-adrenergic receptor antagonism. In a placebo-controlled augmentation trial, Litman *et al.* (1996) demonstrated significant improvement in psychosis and negative symptoms with the a_2-adrenergic receptor antagonist idazoxan when it was added to FGAs. Idazoxan has been shown to increase dopamine levels in the rat medial prefrontal cortex (Hertel *et al.* 1999). In aged rats (Haapalinna *et al.* 2000) and in patients with frontal dementias (Coull *et al.* 1996), a_2-adrenergic receptor blockers have also been reported to improve cognitive functioning. Svensson *et al.* (1995) found that prazosin, an a_1 receptor antagonist, inhibited both the behavioral activation and the increase in mesolimbic dopamine release produced by PCP or MK-801.

In summary, risperidone and paliperidone possess at least two mechanisms that may confer atypical characteristics. 5-HT_{2A} receptor antagonism partially protects against D_2 antagonist-induced neurological side effects and may improve negative symptoms and cognitive functioning via modulation of mesocortical dopamine activity. In addition, blockade of adrenoceptors may further increase prefrontal cortical activity and could increase antipsychotic efficacy by modulating mesolimbic dopamine activity. Unlike other SGA agents, risperidone and paliperidone do not differ from FGAs in their dissociation constant for the D_2 receptor; this feature perhaps accounts for the risk of EPS at high dosages, as well as their greater propensity to cause hyperprolactinemia.

Indications and Efficacy

Risperidone is approved by the FDA for the treatment of schizophrenia, bipolar mania, and irritability associated with autism. In August 2007, the indication for schizophrenia was extended to include adolescents ages 13-17 years, and the bipolar mania indication was extended to include children 10-17 years of age. The risperidone microsphere formulation (Consta long-acting injectable [LAI]) is approved for the treatment of schizophrenia and bipolar I disorder. Extended-release oral paliperidone (Invega) is approved for the treatment of schizophrenia and schizoaffective disorder, LAI paliperidone palmitate (Sustenna) is approved for the treatment of schizophrenia and schizoaffective disorder, and PP3M (Invega Trinza) is approved for the treatment of schizophrenia.

Schizophrenia

Clinical Trial Results for Risperidone

Eight-week trials. In the two North American registration trials (Chouinard *et al.* 1993; Marder and Meibach 1994), a total of 513 patients with chronic schizophrenia were randomly assigned to an 8-week double-blind, fixed-dose, placebo-controlled

comparison of risperidone (2, 6, 10, or 16 mg/day) versus haloperidol (20 mg/day). Risperidone dosages of 6, 10, and 16 mg/day produced significantly greater reductions, as compared with haloperidol, in each of the five domains of the Positive and Negative Syndrome Scale (PANSS), derived by principal component analysis (Marder *et al.* 1997), and significantly higher response rates, defined as a 20% reduction in the PANSS total score. Effect sizes representing the difference in change scores between risperidone (6 mg/day) and haloperidol, although statistically significant, were uniformly small by Cohen's classification system (Cohen 1988): negative symptoms 0.31, positive symptoms 0.26, disorganized thoughts 0.22, uncontrolled hostility/excitement 0.29, and anxiety/depression 0.30 (Table 29-2). Severity of EPS was greater with haloperidol than with risperidone; further statistical analysis suggested that differences in EPS rates did not significantly influence the differences in PANSS subscale ratings (Marder *et al.* 1997). In fact, risperidone 10 mg/day and 16 mg/day produced improvements in negative symptoms equivalent to those seen with risperidone 6 mg/day, despite increased EPS at the higher dosages of risperidone.

TABLE 29-2. Effect sizes on PANSS symptom dimensions: North American trials (*N* = 513)

	Adjusted mean change scores			Risperidone 6 mg/day	
	Placebo	**Risperidone 6 mg/day**	**Haloperidol 20 mg/day**	**Effect size vs. placebo**	**Effect size vs. haloperidol**
PANSS total	[?] 3.8	[?] 18.6	[?] 5.1	0.53	0.31
Negative	0.2	[?] 3.4	[?] 0.1	0.27	0.26
Positive	0.9	[?] 5.7	[?] 2.3	0.48	0.22
Disorganized thought	0.1	[?] 4.6	[?] 0.2	0.43	0.24
Hostility/excitement	0.2	[?] 2.5	[?] 0.1	0.47	0.29
Anxiety/depression	[?] 0.1	[?] 2.5	[?] 0.6	0.36	0.30

Note. PANSS = Positive and Negative Syndrome Scale.
Source. Adapted from Marder *et al.* 1997.

In a comparison of risperidone (1, 4, 8, 12, and 16 mg/day) and haloperidol (10 mg/day) in a large 8-week European trial involving 1,362 subjects with schizophrenia (Peuskens and Risperidone Study Group 1995), PANSS subscale change scores among risperidone-treated subjects indicated a preferential response to daily dosages of 4 mg and 8 mg. However, neither the risperidone group taken as a whole nor individual risperidone dosages achieved significantly better outcomes than haloperidol (10 mg/day) on any measure except for EPS, suggesting that the clinical superiority of risperidone over haloperidol in previous studies may have resulted from excessively high dosing of the comparator.

CATIE. In the National Institute of Mental Health-funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; Stroup *et al.* 2003), 1,432 patients with

chronic schizophrenia were randomly assigned to double-blind, flexibly dosed treatment for 18 months with risperidone, olanzapine, quetiapine, ziprasidone, or the FGA comparator perphenazine. Clinicians could adjust the dosage of each drug by prescribing 1-4 capsules daily; risperidone capsules contained 1.5 mg, and the mean daily dosage administered in the study was 3.9 mg. Based on the primary outcome measure, time to all-cause discontinuation, risperidone was less effective than olanzapine (mean dosage 20 mg/day) and comparable in effectiveness to perphenazine, quetiapine, and ziprasidone (Lieberman *et al.* 2005). Although differences in rates of dropout due to intolerance did not reach statistical significance, risperidone consistently was the best-tolerated drug, particularly for subjects who had discontinued their first assigned drug due to intolerance.

Maintenance treatment. Csernansky *et al.* (2002) randomly assigned 365 patients with stable schizophrenia or schizoaffective disorder to clinician-determined flexible dosing with risperidone or haloperidol for a minimum of 1 year. Kaplan-Meier estimates of the risk of relapse at the end of the study were 34% with risperidone and 60% with haloperidol, a highly significant difference (P = 0.001). The LAI risperidone microsphere formulation (Consta) at fixed dosages of 25 mg, 50 mg, and 75 mg administered biweekly was superior in efficacy to placebo in a 12-week trial (Kane *et al.* 2003), but the 75-mg biweekly dosage was not developed further due to a higher rate of EPS. In a 52-week maintenance study comparing fixed doses of risperidone microspheres administered every 2 weeks, the 25-mg dosage was associated with a relapse rate of 21.6%, and the 50-mg dosage was associated with a 14.9% relapse rate ($P = 0.06$) (Simpson *et al.* 2006). Comparisons of risperidone microspheres against oral SGAs have failed to demonstrate greater benefit with the LAI formulation in randomized trials. In 12-month randomized trials, the efficacy of risperidone microspheres was similar to that of oral risperidone ($n = 50$ [Bai *et al.* 2007]), oral olanzapine ($n = 377$ [Keks *et al.* 2007]), or clinician's choice of an oral antipsychotic other than clozapine ($n = 369$ [Rosenheck *et al.* 2011]). By contrast, a nationwide cohort study using national databases in Norway found risperidone microspheres to be more effective in preventing readmission after a first hospitalization compared with oral risperidone and other oral antipsychotics, with the exception of olanzapine and clozapine (Tiihonen *et al.* 2011). In a subsequent study involving more than 29,000 patients with schizophrenia in Sweden, paliperidone palmitate was the most effective of all studied medications in preventing rehospitalization (Tiihonen *et al.* 2017). Because antipsychotic treatments in these naturalistic studies were not randomized, conclusions are limited; nonetheless, the advantage found with depot formulations may reflect performance under typical clinical conditions.

Cognitive functioning in schizophrenia. Several early studies suggested that risperidone might better improve cognitive functioning, particularly verbal working memory, compared with haloperidol (Green *et al.* 1997; Harvey *et al.* 2005). A large double-blind trial that examined cognitive effects in 414 chronic schizophrenia patients treated for 52 weeks with risperidone (mean dosage 5.2 mg/day), olanzapine (12.3 mg/day), and haloperidol (8.2 mg/day) found no difference between treatments on the composite cognitive score, although risperidone and olanzapine were superior to haloperidol in a secondary analysis of completers (Keefe *et al.* 2006). When compared with low-dose haloperidol (mean dosage 5 mg/day), no cognitive advantage was found for risperidone (Green *et al.* 2002). In addition, in the CATIE, neither risperidone nor any other SGA demonstrated cognitive benefit compared with the FGA agent perphenazine (Keefe *et al.* 2007). A study in medication-naive patients found similar overall cognitive improvement with risperidone and olanzapine (Cuesta *et al.* 2009); however, another study of risperidone in medication-naive patients reported subsequent impairments of spatial working memory (Reilly *et al.* 2006) and procedural memory (Harris *et al.* 2009).

First-episode and treatment-refractory schizophrenia. Risperidone has been found to be well tolerated and effective for subgroups of patients with schizophrenia, including first-episode patients and older adults. In a 4-month double-blind trial comparing risperidone (mean dosage 3.9 mg/day) and olanzapine (mean dosage 11.8 mg/day) in 112 first-episode patients, both treatments were well tolerated, with an overall completion rate of 72% (Robinson *et al.* 2006). Response rates did not differ significantly between risperidone (54%) and olanzapine (44%), although patients who responded to risperidone were significantly more likely to retain their response. A similar study of 198 first-episode patients found no significant difference in response rates between risperidone (57%) and aripiprazole (63%) (Robinson *et al.* 2015). A 12-month double-blind trial comparing oral risperidone with LAI risperidone in 86 patients with recent-onset schizophrenia showed significantly lower relapse rates in the patients receiving the depot formulation (Subotnik *et al.* 2015). However, another randomized controlled trial of 85 first-episode patients found oral SGAs and LAI risperidone to be equally effective and to have similar safety profiles (Malla *et al.* 2016). Further studies with larger samples are probably necessary before treatment with LAI risperidone following a first episode of schizophrenia can be confidently recommended, although these findings indicate that it is a safe and effective option.

Experience with patients with treatment-resistant schizophrenia has been less consistent. In the U.S. multicenter registration study, Marder and Meibach (1994) found that patients who were presumed to have failed to respond to FGAs, on the basis of a history of hospitalization for at least 6 months before study entry, did not respond to haloperidol (20 mg/day) but did display significant response to risperidone (6 mg/day and 16 mg/day) compared with placebo. Wirshing *et al.* (1999) reported significant improvement with risperidone (6 mg/day) compared with haloperidol (15 mg/day) during a 4-week fixed-dose trial of 67 patients with schizophrenia and a history of treatment resistance. In contrast, Volavka *et al.* (2002) found no difference between high-dose risperidone (8-16 mg/day) and haloperidol (10-20 mg/day) in patients established by history to be treatment resistant to FGAs. In the CATIE, risperidone was more effective than quetiapine but did not differ from olanzapine and ziprasidone in patients who discontinued their first-assigned SGA medication due to lack of efficacy (Stroup *et al.* 2006). In contrast, patients who discontinued perphenazine (for any reason) subsequently did better on quetiapine or olanzapine than they did on risperidone (Stroup *et al.* 2007). Two meta-analyses comparing FGAs and SGAs suggested an advantage for risperidone over older drugs (Davis *et al.* 2003; Leucht *et al.* 2009), and a recent network meta-analysis broadly confirmed this suggestion (Leucht *et al.* 2013).

Clinical Trial Results for Paliperidone

In a 6-week trial of acutely ill schizophrenia patients, extended-release paliperidone (Invega) at dosages of 6, 9, and 12 mg/day was more effective than placebo (Kane et al. 2007), and in a flexibly dosed trial (9-15 mg/day), extended-release paliperidone significantly reduced relapse compared with placebo (Kramer *et al.* 2007). Combined results from three placebo-controlled trials involving 1,326 acutely ill patients with schizophrenia found significant improvement with paliperidone across a daily dosage range of 3-15 mg (Meltzer *et al.* 2008). Three studies compared paliperidone with olanzapine 10 mg/day and found no difference in efficacy, but paliperidone was associated with more movement disorders and less weight gain (Nussbaum and Stroup 2008). The network meta-analysis by Huhn *et al.* (2019) concluded that paliperidone was significantly less effective than clozapine but not risperidone, with risperidone and paliperidone displaying similar relationships to other antipsychotics.

LAI paliperidone palmitate administered every 4 weeks has been demonstrated to be more effective than placebo (Hough *et al.* 2010; Kramer *et al.* 2010; Nasrallah *et al.* 2010; Takahashi *et al.* 2013) and to be similar in efficacy to risperidone microspheres administered every 2 weeks (Pandina *et al.* 2011). The latter finding was not replicated in another study (Fleischhacker *et al.* 2012), although paliperidone palmitate dosing was suboptimal. A randomized clinical trial comparing LAI paliperidone palmitate with depot haloperidol administered in a matched loading-dose schedule (McEvoy *et al.* 2014) showed that the two drugs were equally effective in preventing relapse.

A Phase III clinical trial of PP3M (Invega Trinza) versus placebo was terminated early after the interim analysis clearly demonstrated the superior efficacy of PP3M (hazard ratio 3.45; 95% CI: 1.73-6.88; $P < 0.001$) (Berwaerts *et al.* 2015).

A second Phase III randomized, double-blind noninferiority study (N = 1,016) comparing PP3M with paliperidone palmitate 1-month formulation found no differences in efficacy, relapse rates, or side-effect profiles between the two formulations (Savitz *et al.* 2016).

Bipolar Disorder and Treatment-Resistant Major Depressive Disorder

Six controlled trials of 3-4 weeks' duration that included a total of 1,343 patients have examined the efficacy of risperidone as monotherapy or in combination with a mood stabilizer for the acute treatment of bipolar mania (Rendell *et al.* 2006). As monotherapy and in combination, risperidone was more effective than placebo and similar in efficacy to haloperidol but produced more weight gain and fewer EPS (Rendell *et al.* 2006). In a placebo-controlled trial of open-label risperidone LAI microspheres in the maintenance treatment of bipolar I disorder, patients (n = 303) with manic or mixed episodes who maintained response during a preceding 26-week period of LAI risperidone after an initial 3-week period of oral risperidone were randomly allocated to placebo injections or continued treatment with LAI risperidone for up to 24 months. A switch to placebo injections significantly shortened the time to recurrence of manic episodes but not depressive episodes (Quiroz *et al.* 2010).

Risperidone 1-2 mg/day was evaluated as an adjunct to antidepressant therapy in a 4-week placebo-controlled trial in 174 individuals with antidepressant-resistant major depressive disorder recruited from 19 primary care and psychiatric centers (Mahmoud *et al.* 2007). Risperidone produced significantly lowered ratings of depressive symptoms compared with placebo. Remission rates were 25% with risperidone versus

11% with placebo ($P = 0.004$). Risperidone was well tolerated, with an 81% study completion rate (vs. 88% with placebo).

Autism Spectrum Disorder and Intellectual Developmental Disorder

Risperidone also was studied in a large 8-week placebo-controlled trial of 101 children and adolescents (ages 5-17 years) with DSM-IV (American Psychiatric Association 1994)-defined autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior (McCracken *et al.* 2002). Flexible dosing with risperidone (range 0.5-3.5 mg/day; mean dosage 1.2 mg/day) resulted in a mean reduction of 57% in irritability, compared with a decrease of 14% in the placebo group, and the response rate was 69% with risperidone and 12% with placebo. In a study of 32 children (ages 5-17 years) with DSM-IV autistic disorder who were treated for 4 months with open-label risperidone (mean dosage 2 mg/day), those who continued treatment with risperidone during the second study arm, an 8-week double-blind substitution trial, had much lower relapse rates compared with patients who were switched to placebo (Research Units on Pediatric Psychopharmacology Autism Network 2005). Risperidone at a mean dosage of 2 mg/day was also found to be more effective than placebo in a study of 31 adults with DSM-IV autistic disorder or pervasive developmental disorder not otherwise specified (McDougle *et al.* 1998). In these studies, risperidone improved irritability and restricted, repetitive, and stereotyped behavioral problems associated with autism but was not effective for social or language deficits (McDougle *et al.* 2005). Risperidone at a dosage of 0.02-0.06 mg/kg was found to be well tolerated and effective for disruptive behaviors in children with low intelligence (IQ between 36 and 84) in a 6-week placebo-controlled trial (Aman *et al.* 2002); however, a randomized trial of risperidone, haloperidol, and placebo for nonpsychotic, aggressive adult patients with intellectual developmental disorder found no benefit for aggression with either active medication (Tyrer *et al.* 2008).

Other Disorders

Obsessive-Compulsive Disorder

A meta-analysis of antipsychotic augmentation in selective serotonin reuptake inhibitor-refractory OCD including three trials and 77 patients treated with risperidone found an advantage over placebo, with a standardized mean difference (SMD) of [?] 0.53 (Veale *et al.* 2014). Patients taking risperidone were 3.1 times more likely to respond to treatment than patients taking placebo, with a resultant number needed to treat (NNT) of 4.65. In contrast to haloperidol, treatment response was not more common with risperidone in the presence of comorbid tic disorder (McDougle *et al.* 2000).

Posttraumatic Stress Disorder

In a network meta-analysis involving 58 trials and 6,766 patients, risperidone was found to be more effective than placebo in the treatment of PTSD, with an SMD of [?] 0.53 (de Moraes Costa *et al.* 2020). A trial of adjunctive risperidone for patients with combat-related PTSD found improvements in overall sleep quality and a reduction in severity of nightmares (Krystal *et al.* 2016).

Generalized Anxiety Disorder

In a 4-week placebo-controlled add-on trial of low-dose risperidone in 417 patients with persistence of generalized anxiety disorder symptoms despite 8 weeks of anxiolytic therapy, no benefit from risperidone was found in the primary analysis; however, risperidone was associated with greater improvement in patients who had moderate or severe anxiety at baseline (Pandina *et al.* 2007). Risperidone was highly effective for OCD symptoms in a 6-week placebo-controlled trial of 36 adults prospectively confirmed to be nonresponsive to treatment with a selective serotonin reuptake inhibitor (McDougle *et al.* 2000). Symptoms of anxiety and depression also were more responsive to risperidone than to placebo. Fifty percent of risperidone-treated patients responded (mean dosage 2.2 mg/day), compared with none in the placebo group.

Alzheimer's Disease

In the CATIE-Alzheimer's Disease study, risperidone had the longest time to discontinuation due to lack of effectiveness (27 weeks) among the agents studied; comparison results were 22 weeks for olanzapine, 9 weeks for quetiapine, and 9 weeks for placebo (Schneider *et al.* 2006). However, because of poor tolerability, none of the three antipsychotics differed from placebo on time to all-cause discontinuation. Risperidone was associated with a small improvement (SMD [?] 0.26) on the Cohen-Mansfield Agitation Inventory in a network meta-analysis of 17 studies investigating SGA treatment of dementia (Yunusa *et al.* 2019), although the risk of cerebrovascular adverse events was 3.85 times that of placebo. Like all atypical antipsychotics, risperidone and paliperidone carry an FDA black box warning for risk of death in the treatment of older adults with dementia, following a 2005 meta-analysis of randomized controlled trials that showed a 54% increase in mortality over treatment with placebo (Schneider *et al.* 2006).

Side Effects and Toxicology

Risperidone shares class warnings with other SGAs in the United States, including the risks of tardive dyskinesia, neuroleptic malignant syndrome, and hyperglycemia and diabetes, as well as the risk of increased mortality in older adults with dementia-related psychosis. However, risperidone generally has been very well tolerated in clinical trials. In the U.S. multicenter trial reported by Marder and Meibach (1994), only headache and dizziness were significantly more common with risperidone 6 mg/day than with placebo, whereas the group receiving risperidone 16 mg/day treatment also reported more EPS and dyspepsia than did the group receiving placebo (Table 29-3). Fatigue, sedation, accommodation disturbances, orthostatic dizziness, palpitations or tachycardia, weight gain, diminished sexual desire, and erectile dysfunction displayed a statistically significant relationship to risperidone dosage, although most were not significantly elevated compared with placebo. In a flexible-dose relapse prevention study reported by Csernansky *et al.* (2002), no side effects were more common with risperidone compared with haloperidol, although risperidone produced significantly greater weight gain. In a flexibly dosed, placebo-controlled trial of risperidone for children with disruptive behavior, risperidone (mean dosage 1.2 mg/day) produced more somnolence, headache, vomiting, dyspepsia, weight gain, and prolactin elevation than did placebo; most side effects were rated mild to moderate and did not adversely affect compliance (Aman *et al.* 2002).

TABLE 29-3. Side effects reported by patients with schizophrenia receiving placebo, risperidone, or haloperidol in the U.S. multicenter trial

	Percentage of patients			
	Placebo (*n* = 66)	**Risperidone 6 mg (*n* = 64)**	**Risperidone 16 mg (*n* = 64)**	**Haloperidol (*n* = 66)**

[a] $P < 0.05$ versus placebo.

[b] $P < 0.01$ versus placebo.

Source. Adapted from Marder and Meibach 1994.

	Percentage of patients			
	Placebo (n = 66)	**Risperidone 6 mg (n = 64)**	**Risperidone 16 mg (n = 64)**	**Haloperidol (n = 66)**
Insomnia	9.1	12.5	9.4	12.1
Agitation	7.6	10.9	12.5	16.7
Anxiety	1.5	7.8	4.7	1.5
Nervousness	1.5	6.3	1.6	0
Somnolence	0	3.1	9.4[a]	4.5
Extrapyramidal side effects	10.6	10.9	25.0[a]	25.8[a]
Headache	4.5	15.6[a]	9.4	7.6
Dizziness	0	9.4[a]	10.9[b]	0
Dyspepsia	4.5	9.4	6.3	4.5
Vomiting	1.5	6.3	6.3	3.0
Nausea	0	6.3	3.1	1.5
Constipation	0	1.6	6.3	1.5
Rhinitis	6.1	15.6	6.3	4.5
Coughing	1.5	9.4	3.1	3.0
Sinusitis	1.5	6.3	1.6	0
Fever	0	6.3	3.1	1.5
Tachycardia	0	4.7	6.3	1.5

[a] $P < 0.05$ versus placebo.

[b] $P < 0.01$ versus placebo.

Source. Adapted from Marder and Meibach 1994.

Metabolic Effects

Weight gain with risperidone is intermediate; that is, the degree of weight gain is between that associated with agents such as molindone, amisulpride, and ziprasidone, which appear to be relatively weight neutral, and that associated with agents such as clozapine, olanzapine, and low-potency phenothiazines (Rummel-Kluge *et al.* 2010; Sikich *et al.* 2008). In a meta-analysis of controlled trials, Allison *et al.* (1999), using a random effects model, estimated the mean weight gain at 10 weeks with risperidone to be 2.0 kg, compared with 0.5 kg with haloperidol, 3.5 kg with olanzapine, and 4.0 kg with clozapine. In the CATIE, in which risperidone had the lowest rate of discontinuation due to side effects, risperidone treatment was associated with a mean monthly weight gain of 0.4 lb, olanzapine with 2.0 lb, and quetiapine with 0.5 lb; by contrast, perphenazine and ziprasidone were associated with a mean monthly weight *loss* of 0.2 lb and 0.3 lb, respectively (Lieberman *et al.* 2005). Although determining the risk for hyperglycemia is complex, and results of studies have not been completely consistent, it appears that risperidone does not produce insulin resistance to the degree associated with olanzapine and clozapine (American Diabetes Association *et al.* 2004; Henderson *et al.* 2006; Lieberman *et al.* 2005). A meta-analysis of head-to-head comparisons of SGAs found that risperidone produced more cholesterol elevation than aripiprazole and ziprasidone and less elevation than olanzapine and quetiapine (Rummel-Kluge *et al.* 2010). Metabolic side effects in children tend to be more severe than those in adults; for example, in one study of pediatric patients younger than 20 years, risperidone produced a mean weight gain of 5.3 kg (11.7 lb) over the 12-week treatment period (Correll *et al.* 2009). Metabolic side effects with paliperidone appear to be similar to those with risperidone.

Extrapyramidal Side Effects

Significant reductions in EPS with risperidone compared with high-dose haloperidol were a consistent finding in the North American trials (Chouinard *et al.* 1993; Marder and Meibach 1994). Measurement of EPS in the placebo group was complicated because 25% of the subjects were receiving depot antipsychotics before enrollment. Risperidone produced significantly fewer parkinsonian side effects than did haloperidol (20 mg/day), based on several measures, including self-report, change scores on the Extrapyramidal Symptom Rating Scale, and use of anticholinergic medication. Patients receiving risperidone 2 mg/day and 6 mg/day did not differ from the group receiving placebo in mean ratings of parkinsonism and in the use of anticholinergic medication. Parkinsonism change scores were significantly correlated with risperidone dosage ($r = 0.94$); however, risperidone at 16 mg/day was associated with fewer parkinsonian side effects than was haloperidol. Dystonia occurred in six of the patients treated with risperidone (1.7%) and two of the patients treated with haloperidol (2.4%). Dystonia rates did not differ between treatment groups, and the rates did not exhibit a relationship to risperidone dosage.

In the large European multicenter trial, maximum ratings of parkinsonism, hyperkinesis, and dystonia were greater with haloperidol (10 mg/day) than with all dosages of risperidone (maximum of 12 mg/day), and anticholinergic dosing was accordingly higher in the group treated with haloperidol (Peuskens and Risperidone Study Group 1995). Similarly, in a flexible-dose comparison of risperidone (mean dosage 4.9 mg/day) and haloperidol (mean dosage 11.7 mg/day) for prevention of relapse, EPS rates and use of anticholinergic medication significantly favored the group taking risperidone (Csernansky *et al.* 2002). However, in a smaller double-blind, flexible-dose trial comparing risperidone (5-15 mg/day) and the moderate-potency FGA agent perphenazine (16-48 mg/day) in 107 patients, no difference in EPS rates was observed (Hoyberg *et al.* 1993), indicating that the potency of the comparator agent may in part determine the relative benefit of risperidone for EPS. Of interest, in a study of low-dose risperidone (mean dosage 1.2 mg/day) in children with behavioral disorders, ratings of EPS did not differ between risperidone and placebo (Aman *et al.* 2002). No differences in EPS ratings were found between any treatment groups in the CATIE (Lieberman *et al.* 2005), although discontinuation rates due to EPS significantly differed, with perphenazine producing the highest discontinuation rate (8%) and olanzapine (2%), risperidone (3%), and quetiapine (3%) producing the lowest.

The experience with tardive dyskinesia (TD) in individuals treated with risperidone has been promising. Jeste *et al.* (1999) randomly assigned 122 older adults to either low-dosage haloperidol (median daily dosage 1 mg) or risperidone (median daily dosage 1 mg). The very high rates of treatment-emergent TD typically found in older adults made this sample a sensitive assay for TD risk. After 9 months, rates of treatment-emergent TD were 30% with haloperidol versus less than 5% with risperidone. Risperidone was also noted to decrease dyskinetic movements compared with haloperidol in a Canadian multicenter trial reported by Chouinard *et al.* (1993), and it was associated with a treatment-emergent TD rate of 0.6%, compared with a rate of 2.7% with haloperidol, in a relapse prevention trial reported by Csernansky *et al.* (2002).

Hyperprolactinemia

Unlike other SGA agents, risperidone and paliperidone substantially increase serum prolactin levels. In the previously cited network meta-analysis by Huhn *et al.* (2019), paliperidone and risperidone were the two agents responsible for the greatest prolactin elevations, differing significantly from every treatment other than amisulpride. There is some evidence that prolactin levels may decrease over time (Eberhard *et al.* 2007; Findling *et al.* 2003-2Kleinberg *et al.* (1999) analyzed combined results from the North American and European multicenter registration trials, which included plasma prolactin concentrations from 841 patients and clinical ratings of symptoms associated with hyperprolactinemia from 1,884 patients. Mean prolactin levels significantly correlated with risperidone dosage; risperidone 6 mg/day produced elevations roughly comparable to those seen with haloperidol 20 mg/day and significantly higher than those seen with haloperidol 10 mg/day. The combined incidence of amenorrhea and galactorrhea in women, which varied between 8% and 12%, was similar for all dosages of risperidone and haloperidol (10 mg/day). Because symptom frequencies were available only for 14 women treated with placebo, comparisons with placebo were not informative. Sexual dysfunction or gynecomastia occurred in 15% of men treated with risperidone (4-6 mg/day), compared with 14% of men treated with haloperidol (10 mg/day) and 8% of men in the placebo group. Compared with placebo, ejaculatory dysfunction was significantly more common only in the group treated with risperidone (12-16 mg/day). Mean plasma prolactin levels were not significantly related to clinical side effects for either men or women. Decreased libido also did not differ between treatment groups and did not correlate with plasma prolactin levels. In the CATIE, prolactin levels increased by a mean of 15.4 ng/mL with risperidone, compared with a 0.4 ng/mL mean elevation with perphenazine and decreases of 4.5-9.3 ng/mL with the other SGAs (Lieberman *et al.* 2005). Despite having significantly higher serum prolactin concentrations, patients treated with risperidone did not report significantly higher rates of sexual dysfunction, gynecomastia, galactorrhea, or irregular menses.

Two reports of clinical trials with extended-release paliperidone have indicated low levels of prolactin-related side effects (1% and 4%) (Kane *et al.* 2007; Kramer *et al.* 2007). However, in the one publication that reported prolactin levels, substantial increases in mean plasma prolactin concentrations were observed (men: 17.4 ng/mL at baseline to 45.3 ng/mL at week 6; women: 38.0 ng/mL to 124.5 ng/mL) (Kane *et al.* 2007). A 13-week comparison of paliperidone palmitate with risperidone microspheres reported that paliperidone palmitate was associated with moderately higher elevations from baseline in prolactin levels compared with risperidone (women: 21.8 vs. 15.6 ng/mL; men: 9.4 vs. 6.0 ng/mL) (Pandina *et al.* 2011); however, another study found that the proportion of patients with abnormally elevated prolactin levels was higher in the group receiving LAI risperidone than in that receiving paliperidone palmitate (Fleischhacker *et al.* 2012). Two preliminary studies with risperidone found that plasma prolactin concentrations correlated with 9-hydroxyrisperidone (paliperidone) concentrations and not with risperidone concentrations (Melkersson 2006; Troost *et al.* 2007). The ratio of 9-hydroxyrisperidone levels to risperidone levels also correlated with prolactin concentration (Troost *et al.* 2007); in agreement with this finding, rapid metabolizers of CYP2D6 were found to have higher prolactin concentrations than poor metabolizers (Troost *et al.* 2007).

Cardiovascular Effects

Because of its high affinities for adrenoreceptors, risperidone would be expected to produce orthostatic hypotension. However, with a 3-to 7-day dosage escalation schedule, initial postural hypotension and tachycardia have been avoided in clinical trials, with only rare cases of hypotension and syncope reported (Chouinard *et al.* 1993; Marder and Meibach 1994). Risperidone has very modest effects on cardiac conduction. No significant prolongation of the QTc interval was detected at dosages of up to 25 mg/day in early safety trials, and no relationship between QTc interval and risperidone dosage was apparent (Mesotten *et al.* 1989). A mean QTc prolongation of 10 milliseconds, measured after peak absorption of risperidone (16 mg/day), was found in a study comparing SGAs and FGAs, according to data filed with the FDA by Pfizer Inc. (Harrigan *et al.* 2004). In a retrospective cohort study of Medicaid enrollees in Tennessee, risperidone was associated with a 2.9-fold increase in rate of sudden cardiac death, compared with a 1.61-fold increase with haloperidol and a 3.67-fold increase with clozapine (Ray *et al.* 2009).

High Dosage and Overdose

Mesotten *et al.* (1989) reported the results of a safety trial involving 17 inpatients with psychosis in which, after a washout of previous medication, risperidone was started at 10 mg/day, and the dosage was then increased weekly by 5 mg/day to a maximum of 25 mg/day. Despite extremely high dosages, sedation was the only prominent side effect. Although risperidone does not bind significantly to muscarinic cholinergic receptors, transient dry mouth, blurred vision, and urinary retention were observed in individual subjects. Palpitations occurred in two subjects. Heart rate significantly increased during the trial, and blood pressure slightly decreased; however, no cases of significant hypotension were reported. An endocrine battery, including plasma triiodothyronine, thyroid-stimulating hormone, growth hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, and cortisol levels, was performed, and only prolactin was found to be affected.

Reported overdoses with risperidone have generally been benign, with moderate QT prolongation and no serious cardiac complications (Brown *et al.* 1993; Lo Vecchio *et al.* 1996).

Drug-Drug Interactions

Because CYP2D6 status affects the half-life of risperidone and the relative ratio of risperidone to 9-hydroxyrisperidone in plasma, the total serum concentration of the

"active moiety," or the sum of the concentrations of risperidone and 9-hydroxyrisperidone, may be significantly increased with addition of a CYP2D6 inhibitor (e.g., fluoxetine) in rapid metabolizers but not in poor metabolizers (Bondolfi *et al.* 2002; Spina *et al.* 2002). In one study of nine patients treated with risperidone, the addition of fluoxetine resulted in a 75% increase in blood levels of the active moiety (risperidone plus 9-hydroxyrisperidone); two patients developed parkinsonian side effects (Spina *et al.* 2002). Paliperidone plasma concentrations are not influenced by CYP2D6 status, nor are paliperidone plasma concentrations likely to be affected by drug-drug interactions. It has been hypothesized that the addition of a CYP2D6 inhibitor (e.g., fluoxetine) could decrease risperidone-induced prolactin elevation by increasing the ratio of risperidone to 9-hydroxyrisperidone (Troost *et al.* 2007), although this has not been rigorously tested.

Conclusion

Risperidone was the first antipsychotic agent developed specifically to exploit the clinical advantages of combined D_2 and $5\text{-}HT_{2A}$ receptor antagonism. a-Adrenergic antagonism additionally may contribute to the antipsychotic and potentially cognition-enhancing effects of risperidone. Risperidone's active metabolite, paliperidone, is pharmacologically quite similar to the parent drug and comprises roughly 80%-90% of the serum concentration of the active moiety (risperidone + paliperidone) in most patients treated with risperidone. Risperidone and paliperidone are generally quite well tolerated, producing moderate weight gain and mild sedation. Initial dosage titration is necessary to prevent orthostatic blood pressure changes and dizziness, although this may be less necessary with extended-release paliperidone. EPS are dose related and are typically less common with risperidone than with haloperidol but more common with risperidone than with other SGAs. Risperidone and paliperidone markedly elevate prolactin levels, although the relationship between plasma prolactin concentrations and clinical symptoms is complex. The efficacy of risperidone was initially established in comparison with high-dose haloperidol, against which it was significantly more effective for all five symptom clusters derived from the PANSS. However, the magnitude of difference in effect size was not large for individual symptom clusters. In the CATIE, risperidone (at a mean daily dosage of 3.9 mg) did not differ from perphenazine in rates of discontinuation due to lack of effectiveness but was less effective than olanzapine (Lieberman *et al.* 2005). The risperidone microsphere product was the first FDA-approved SGA long-acting intramuscular formulation, and paliperidone palmitate was the first SGA depot formulation that could be administered at an interval of every 4 weeks. PP3M is the first depot antipsychotic that can be administered on a quarterly schedule. Overall, risperidone and paliperidone are well-tolerated SGA agents with efficacy comparable to that of most other agents in their class.

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CHAPTER 30

Aripiprazole and Brexpiprazole

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In this chapter, we review the preclinical and clinical pharmacology of aripiprazole and brexpiprazole, two novel atypical (second-generation) antipsychotics.

History and Discovery

Aripiprazole is a dihydroquinolinone antipsychotic agent. Chemically, it is unrelated to phenothiazines, butyrophenones, or thienobenzodiazepines. Pharmacologically, it was the first antipsychotic to exhibit a novel mechanism of action, combining partial agonist activity at dopamine type 2 (D_2), dopamine type 3 (D_3), and serotonin type 1A (5-HT_{1A}) receptors with antagonist activity at serotonin type 2A (5-HT_{2A}) and D_2 receptors (Burris *et al.* 2002; Jordan *et al.* 2002). Aripiprazole represents a significant innovation, following the introduction of typical (first-generation) and atypical antipsychotics, in the pharmacology of therapeutic agents for psychotic disorders.

The development of aripiprazole was guided by prevailing hypotheses of the etiology of schizophrenia. The dopamine hypothesis (Seeman and Niznik 1990) proposes that abnormalities in dopaminergic neurotransmission in the brain cause the symptoms of schizophrenia and suggests that schizophrenia involves a biphasic disturbance in dopaminergic pathways (Davis *et al.* 1991; Pycock *et al.* 1980; Weinberger 1987). Underactivity of the mesocortical dopaminergic pathway leads to hypodopaminergic activity in the frontal cortex, whereas overactivity in the mesolimbic pathway causes increased dopaminergic neurotransmission. The latter is presumed to cause positive or psychotic symptoms, whereas the former is believed to underlie negative symptoms and cognitive impairment. Another influential hypothesis suggests that the activity of dopaminergic pathways is modulated by serotonergic neurons. In the striatum, serotonin (5-hydroxytryptamine; 5-HT) release inhibits dopamine, whereas in the frontal cortex 5-HT release has a modulatory effect on pyramidal neurons and can affect glutamate release.

Most typical and atypical antipsychotic agents behave as full D_2 receptor antagonists. Their actions in the mesolimbic pathway would therefore be expected to benefit patients with schizophrenia by reducing positive symptoms. However, D_2 receptor antagonism in the other dopaminergic pathways would be expected to cause unwanted side effects, including exacerbation of negative symptoms (mesocortical pathways), extrapyramidal side effects (EPS) and tardive dyskinesia (nigrostriatal tract), and hyperprolactinemia (tuberoinfundibular pathway).

The serotonin hypothesis may explain why the atypical agents, which have antagonist activity at 5-HT_{2A} receptors, are associated with fewer EPS and do not exacerbate (and, in fact, partially alleviate) negative symptoms and cognitive impairment (Leysen *et al.* 1993; Millan 2000; Rao and Moller 1994; Richelson 1999).

On the basis of aripiprazole's pharmacodynamic profile--partial agonist activity at both dopaminergic (D_2 [Burris *et al.* 2002]) and serotonergic (5-HT_{1A} [Jordan *et al.* 2002]) receptors and full antagonist activity at 5-HT_{2A} receptors (McQuade *et al.* 2002)--it was anticipated that aripiprazole treatment would be associated with a reduced burden of unwanted D_2 antagonist activity in the mesocortical, nigrostriatal, and tuberoinfundibular pathways.

Aripiprazole was initially discovered by scientists at Otsuka Pharmaceutical and was first FDA approved for the treatment of schizophrenia in November 2002. Aripiprazole obtained additional FDA indications for manic and mixed episodes associated with bipolar I disorder in 2004, adjunctive treatment of major depressive disorder (MDD) in 2007, irritability associated with autism in 2009, and Tourette's disorder in 2014 (Otsuka Pharmaceutical 2020a). In February 2013, the FDA approved a long-acting depot injectable formulation of aripiprazole for the treatment of schizophrenia. In 2018 this formulation was also approved by the FDA for monotherapy in maintenance treatment of bipolar I disorder (Otsuka Pharmaceutical 2020b). In October 2015, the FDA approved aripiprazole lauroxil, a second long-acting formulation of aripiprazole, for the treatment of schizophrenia (Alkermes 2021a).

Brexpiprazole was first synthesized by Otsuka Pharmaceutical and developed in collaboration with H. Lundbeck A/S with the goal of optimizing its intrinsic activity at D_2 receptors. The pharmacological profile of brexpiprazole is similar to that of aripiprazole, including combined partial agonist activity at D_2, D_3, and 5-HT_{1A} receptors with antagonist activity at 5-HT_{2A} and D_2 receptors. However, brexpiprazole has lower intrinsic activity at D_2 receptors, high-potency partial agonism at 5-HT_{1A} receptors, and stronger antagonism at 5-HT_{2A} receptors (Maeda *et al.* 2014b). Its reduced intrinsic activity at D_2 receptors and stronger antagonism at 5-HT_{2A} receptors relative to aripiprazole suggest a lower potential to induce D_2 partial agonist-mediated effects (i.e., akathisia, insomnia, nausea, and restlessness) and D_2 antagonist effects

(e.g., dystonias, tardive dyskinesia, and hyperprolactinemia) (Fleischhacker 2005; Maeda *et al.* 2014a). Brexpiprazole was approved by the FDA in 2015 for the treatment of schizophrenia and as an adjunctive therapy with antidepressants for the treatment of MDD (Otsuka Pharmaceutical 2023). In 2023, brexpiprazole received supplemental approval for the treatment of agitation associated with dementia due to Alzheimer's disease, becoming the first medication in the United States to have such an indication (U.S. Food and Drug Administration 2023).

Structure-Activity Relations and Pharmacological Profile

Aripiprazole

Aripiprazole--7-{4-(4-[2,3-dichlorophenyl]-1-piperazinyl)butoxy}-3,4-dihydrocarbostyril, a dihydroquinolinone (Figure 30-1)--exhibits potent partial agonist activity at D_2 (Burris *et al.* 2002) and 5-HT_{1A} (Jordan *et al.* 2002) receptors, together with potent antagonist activity at 5-HT_{2A} receptors. It also has high affinity for D_3 receptors; moderate affinity for dopamine type 4 (D_4), serotonin type 2C (5-HT_{2C}), serotonin type 7 (5-HT_7), a_1-adrenergic, and histamine type 1 (H_1) receptors and the serotonin transporter; and negligible affinity for cholinergic muscarinic receptors (Table 30-1). The active metabolite of aripiprazole, dehydroaripiprazole, exhibits a similar affinity at D_2 receptors and has not been shown to have a pharmacological profile that is clinically significantly different from that of the parent compound.

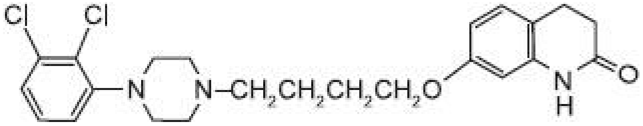

FIGURE 30-1. Chemical structure of aripiprazole.

TABLE 30-1. Receptor-binding profile of aripiprazole

Receptor type	K_i (nM)
Dopaminergic	
D_1	265.0

Note. IC_{50} = half-maximal inhibitory concentration; K_i = inhibition constant.

Source. Adapted from McQuade *et al.* 2002; Otsuka Pharmaceutical 2020a, 2020b.

Receptor type	**K$_i$ (nM)**
D_2	0.34
D_3	0.8
D_4	44.0
D_5	95.0
Serotonergic	
5-HT$_{1A}$	1.7
5-HT$_{2A}$	3.4
5-HT$_{2C}$	15.0
5-HT$_6$	214.0
5-HT$_7$	39.0
Serotonin transporter	98.0
Histaminergic	
H_1	61.0
Adrenergic	
a_1	57.0
Muscarinic	
M_1	IC$_{50}$ (nM) > 1,000

Note. IC$_{50}$ = half-maximal inhibitory concentration; K$_i$ = inhibition constant.

Source. Adapted from McQuade *et al.* 2002; Otsuka Pharmaceutical 2020a, 2020b.

Brexpiprazole

Brexpiprazole--7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1H)-one (Figure 30-2)--exhibits potent partial agonist properties at 5-HT$_{1A}$, D_2, and D_3 receptors. This is combined with potent antagonist activity at 5-HT$_{2A}$ receptors and a_{1B}/a_{2C} adrenoceptors. It also displays antagonistic properties at serotonin type 2B (5-HT_{2B}) and serotonin type 7A (5-HT_{7A}) receptors and moderate-potency antagonism at H_1 receptors. Brexpiprazole has negligible affinity for cholinergic muscarinic receptors (Table 30-2) (Maeda *et al.* 2014a; Otsuka Pharmaceutical 2023).

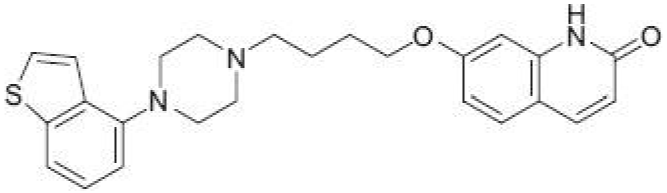

FIGURE 30-2. Chemical structure of brexpiprazole.

TABLE 30-2. Receptor-binding profile of brexpiprazole

Receptor type	K_i (nM)
Dopaminergic	
D_2	0.30
D_3	1.1
Serotonergic	
5-HT_{1A}	0.12
5-HT_{2A}	0.47
5-HT_{2B}	1.9
5-HT_7	3.7
Histaminergic	
H_1	19.0
Adrenergic	
a_{1A}	3.8

Note. K_i = inhibition constant.

Source. Adapted from Maeda *et al.* 2014a; Otsuka Pharmaceutical 2023.

Receptor type	K_i (nM)
a_{1B}	0.17
a_{1D}	2.6
a_{2C}	0.59
Muscarinic	
M_1	67% at 10 mM

Note. K_i = inhibition constant.

Source. Adapted from Maeda *et al.* 2014a; Otsuka Pharmaceutical 2023.

Pharmacokinetics and Disposition

Aripiprazole

Aripiprazole is available for oral administration as tablets in strengths of 2, 5, 10, 15, 20, and 30 mg. Aripiprazole orally disintegrating tablets are available in strengths of 10 and 15 mg, and an oral solution of 1 mg/mL is available. The effective dosage range is 10-30 mg/day for patients with schizophrenia and 15-30 mg/day for patients with bipolar I disorder. For adjunctive treatment of MDD and irritability associated with autism spectrum disorder, the recommended dosage range is 2-15 mg/day. For Tourette's disorder, body weight-based dosing of 2-10 mg/day for patients weighing less than 50 kg and 2-20 mg/day for patients weighing 50 kg or more is indicated.

Oral aripiprazole is available with an embedded ingestible event marker (Abilify MyCite), meant to track drug ingestion and monitor compliance (Otsuka Pharmaceutical 2017). The tablets have an embedded ingestible sensor that records that the medication was taken. The system works by sending a message from the tablet sensor to a wearable patch. The patch transmits the information to a mobile application so that patients can track the ingestion of their medication on their smart phone (U.S. Food and Drug Administration 2017). Patients can also permit their caregivers to access the information through a web-based portal. However, there are no head-to-head studies showing improved medication adherence with the use of the MyCite formulation (Cosgrove *et al.* 2019).

Of note, several aripiprazole formulations were withdrawn from the market by the manufacturer in 2015 for reasons unrelated to efficacy, safety, or tolerability. Unavailable formulations include the aripiprazole oral disintegrating tablet at the 20-mg and 30-mg strengths and the short-acting intramuscular injection.

Aripiprazole is taken once daily with or without food and is well absorbed after oral administration, with peak plasma concentrations occurring within 3-5 hours. Absolute oral bioavailability is 87%. In plasma, aripiprazole and its major metabolite, dehydroaripiprazole, are both more than 99% bound to proteins, primarily albumin. Aripiprazole is extensively distributed outside the vascular system, and studies in humans demonstrating dose-dependent occupancy of D_2 receptors have confirmed that aripiprazole penetrates the brain. Elimination half-lives for aripiprazole and dehydroaripiprazole are 75 hours and 94 hours, respectively (Otsuka Pharmaceutical 2020a).

The aripiprazole depot formulation consists of a lyophilized powder of unmodified aripiprazole that is reconstituted in water and injected into the gluteal or deltoid muscle (Otsuka Pharmaceutical 2020b). The product is available in 300-mg and 400-mg vials, and the effective dosage range is 300-400 mg once monthly. The median peak plasma concentration is reached after 5-7 days. It is recommended that oral aripiprazole supplementation (at 10-20 mg/day) or an alternative antipsychotic be continued for 2 weeks after the first administered injection of long-acting aripiprazole. The mean terminal half-lives of the 300-mg and 400-mg doses are 29.9 and 46.5 days, respectively. Steady-state plasma concentrations are attained after the fourth dose (Otsuka Pharmaceutical 2020b). The aripiprazole once-monthly intramuscular dose of 400 mg with supplemental oral aripiprazole 10 mg/day for the first 2 weeks produces a pharmacokinetic profile consistent with multiple daily dosing of aripiprazole 10-30 mg, with a maximum plasma concentration comparable to that of the 30 mg/day dosage and a minimum plasma concentration comparable to that of the 10 mg/day dosage (Mallikaarjun *et al.* 2013).

Aripiprazole lauroxil, a prodrug of aripiprazole, initially undergoes enzyme-mediated hydrolysis to *N*-hydroxymethyl aripiprazole and then undergoes water-mediated hydrolysis to aripiprazole, the active form. The effective dosage range of aripiprazole lauroxil is 441 mg or 662 mg administered monthly, 882 mg administered monthly or every 6 weeks, and 1,082 mg administered every 2 months. After a single intramuscular injection, aripiprazole appears in systemic circulation within 5-6 days. Aripiprazole lauroxil reaches steady state after four consecutive monthly injections. Mean terminal half-life ranges from 53.9 days to 57.2 days (Alkermes 2021a).

Aripiprazole lauroxil may be initiated in two ways, the first being administration of oral aripiprazole supplementation for 3 weeks after the first administered injection. The second way to initiate aripiprazole lauroxil is with the NanoCrystal Dispersion formulation, which is given as a one-time 675-mg injection in conjunction with one dose of oral aripiprazole 30 mg and the first dose of aripiprazole lauroxil (441, 662, 882, or 1,082 mg). An intramuscular injection of aripiprazole lauroxil, a 30-mg dose of oral aripiprazole, and a single 675-mg dose of aripiprazole lauroxil NanoCrystal Dispersion resulted in aripiprazole concentrations comparable to those from aripiprazole lauroxil treatment initiated with 21 days of oral aripiprazole (Alkermes 2021a, 2021b).

Aripiprazole is metabolized primarily in the liver. Two hepatic cytochrome P450 (CYP) enzymes, 2D6 and 3A4, catalyze its dehydrogenation to dehydroaripiprazole. The active metabolite accounts for 40% of drug exposure, but the predominant circulating moiety is the parent drug. Aripiprazole does not undergo direct glucuronidation and is not a substrate for the following CYP enzymes: 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2E1. Interactions with inhibitors or inducers of these enzymes, or with chemicals related to cigarette smoke, are therefore unlikely to occur.

Brexpiprazole

Brexpiprazole is available for oral administration as tablets with strengths ranging from 0.25 to 4 mg. Ninety-five percent of the estimated maximum efficacy is obtained at a dosage of 3.36 mg/day (Leucht *et al.* 2020). The effective dosage range is 2-4 mg/day for treatment of schizophrenia, 1-3 mg/day for adjunctive treatment of MDD, and 2-3 mg/day for agitation associated with dementia due to Alzheimer's disease.

Brexpiprazole is taken once daily with or without food and is well absorbed after oral administration, with peak plasma concentrations occurring within 4 hours. Absolute oral bioavailability is 95%. Brexpiprazole is highly bound to serum albumin and a_1-acid glycoprotein (> 99%). Elimination half-lives for brexpiprazole and DM-3411, its major metabolite, are 91 hours and 86 hours, respectively (Otsuka Pharmaceutical 2023).

Brexpiprazole is metabolized primarily through the liver by CYP enzymes 2D6 and 3A4. At steady state (which is reached in 10-12 days), the inactive metabolite DM-3411 represents 23%-48% of brexpiprazole's area under the time-concentration curve in plasma (Otsuka Pharmaceutical 2023). Dosage adjustment (a maximum of 2 mg/day for major depressive disorder and of 3 mg/day for schizophrenia) is also recommended for patients with moderate to severe hepatic or renal impairment (Otsuka Pharmaceutical 2023).

Mechanism of Action

Aripiprazole and brexpiprazole both have partial agonist activity at D_2 receptors. The activity of aripiprazole and brexpiprazole at D_2 receptors has been studied in animal models of schizophrenia (Kikuchi *et al.* 1995; Maeda *et al.* 2014b). Hyperdopaminergic activity, seen in rats with repetitive stereotyped behavior induced by apomorphine, is inhibited by both aripiprazole and brexpiprazole (Kikuchi *et al.* 1995; Maeda *et al.* 2014a). These agents may therefore be expected to inhibit hyperdopaminergic activity in the mesolimbic pathway of patients with schizophrenia, thereby (like other available agents) exerting antipsychotic action against the positive symptoms of schizophrenia. On the other hand, in animal models of hypodopaminergic activity, such as the reserpinized rat, both aripiprazole and brexpiprazole have D_2 receptor agonist activity (Maeda *et al.* 2014b). Because aripiprazole and brexpiprazole may postsynaptically exert either D_2 antagonist activity under hyperdopaminergic conditions or D_2 agonist activity under hypodopaminergic conditions, they may be less likely than other antipsychotics to cause excessive D_2 receptor antagonism. In preclinical studies, brexpiprazole showed lower intrinsic activity at D_2 receptors, which suggests a reduced propensity to cause D_2 agonist-associated side effects such as nausea, insomnia, and akathisia (Maeda *et al.* 2014a, 2014b). It is possible that this lower activity may diminish the effects of excess D_2 receptor antagonism, including EPS. No comparative clinical trials of aripiprazole and brexpiprazole have yet been conducted.

Both aripiprazole and brexpiprazole may offer further therapeutic benefits through modulation of central serotonergic pathways. Preclinical studies demonstrated that aripiprazole and brexpiprazole have antagonist activity at 5-HT_{2A} receptors (Maeda *et al.* 2014b; McQuade *et al.* 2002), a characteristic that has been associated with reductions in EPS (Meltzer 1999) and in negative symptoms. In vitro studies also have shown that both aripiprazole and brexpiprazole have partial agonist activity at 5-HT_{1A} receptors (Jordan *et al.* 2002; Maeda *et al.* 2014b), a feature that has been associated with improvement in negative, cognitive, depressive, and anxiety symptoms (Millan 2000).

The side effects of nausea and vomiting may be explained by the dopamine agonist effects of aripiprazole and brexpiprazole, whereas orthostatic hypotension and mild

sedation or weight gain are probably related to these agents' antagonist activity at a_1-adrenergic and H_1 receptors, respectively.

Indications and Efficacy

Aripiprazole

In the United States, aripiprazole is approved by the FDA for treatment of schizophrenia in adults and in adolescents ages 13-17 years, acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate in adults and pediatric patients ages 10-17 years, maintenance treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate in adults, use as an adjunct to antidepressant treatment in adults with MDD who have had an inadequate response to antidepressant therapy, treatment of irritability associated with autism spectrum disorder in pediatric patients ages 6-17 years, and treatment of Tourette's disorder in pediatric patients ages 6-18 years. Aripiprazole is currently available in two formulations for long-acting injectable depot maintenance and relapse management of schizophrenia in adults. Aripiprazole long-acting depot injection is approved for maintenance monotherapy treatment of bipolar I disorder in adults. Additionally, a short-acting intramuscular aripiprazole injection is approved for the acute treatment of agitation associated with schizophrenia or bipolar disorder (manic or mixed) in adults; however, this formulation is no longer available.

Schizophrenia

Aripiprazole's efficacy in the treatment of an acute symptom relapse in schizophrenia was demonstrated in four short-term (4-week) double-blind, placebo-controlled studies. Among these was a pivotal Phase III parallel-group multicenter study with four treatment arms comparing aripiprazole (15 or 30 mg/day) with placebo (Kane *et al.* 2002). Aripiprazole at either dosage produced statistically significant improvements from baseline on Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) Scale scores by week 2. This trial suggested that at daily dosages of 15 mg and 30 mg, aripiprazole provides effective symptom control for patients experiencing an acute exacerbation of schizophrenia symptoms.

In another short-term multicenter Phase III study involving acute symptom relapse in schizophrenia or schizoaffective disorder (Potkin *et al.* 2003), patients were randomly assigned to receive aripiprazole 20 mg/day, aripiprazole 30 mg/day, risperidone 6 mg/day, or placebo for 4 weeks. Compared with placebo, aripiprazole (at both dosages) and risperidone produced statistically significant improvements in scores on standard scales designed to measure antipsychotic efficacy.

The antipsychotic efficacy of aripiprazole in acute symptom relapse in schizophrenia was also demonstrated in two Phase II dose-ranging studies. Patients were randomly assigned to receive aripiprazole 2, 10, or 30 mg/day or haloperidol 10 mg/day (Daniel *et al.* 2000). All three dosages of aripiprazole produced improvements from baseline on efficacy measures, and the 30 mg/day dosage produced statistically significantly greater improvement compared with placebo on all illness scores. Similarly, in a Phase II dosage titration study, aripiprazole 5-30 mg/day was superior to placebo in improving Brief Psychiatric Rating Scale (BPRS) Total, BPRS Core, CGI-Severity, and PANSS-Total scores (Petrie *et al.* 1997).

Results from the three 4-week fixed-dosage studies discussed above (Daniel *et al.* 2000; Kane *et al.* 2002; Petrie *et al.* 1997) were pooled for analysis with those from a 6-week placebo-controlled, fixed-dosage study of aripiprazole at 10, 15, or 20 mg/day (Lieberman *et al.* 2002). The pooled analysis, involving 898 patients randomly assigned to receive aripiprazole, showed that at all investigated dosages greater than 2 mg/day, aripiprazole exhibited antipsychotic efficacy superior to that of placebo. Onset of effect was rapid, with improvement in psychometric scores detectable within 1 week of starting treatment. These pooled efficacy results demonstrate that dosages of 10-30 mg/day represent an effective therapeutic range for aripiprazole treatment.

Two long-term double-blind, randomized controlled multicenter trials yielded further confirmation of aripiprazole's efficacy. A 26-week placebo-controlled study of patients with chronic stable schizophrenia investigated the efficacy of aripiprazole 15 mg/day in relapse prevention (Pigott *et al.* 2003). Aripiprazole treatment significantly increased the time to relapse and resulted in significantly fewer relapses compared with placebo (34% vs. 57%). From week 6 of therapy, PANSS-Total and PANSS-Positive subscale scores showed significantly greater improvement with aripiprazole than with placebo.

In a 52-week study (Kasper *et al.* 2003), patients with schizophrenia who were experiencing an acute symptom relapse were randomly assigned to receive aripiprazole 30 mg/day or haloperidol 10 mg/day. Significantly more aripiprazole-treated patients than haloperidol-treated patients were still taking the medication and responding to treatment at weeks 8, 26, and 52. Both treatments produced sustained improvements from baseline on PANSS-Total and PANSS-Positive subscale scores. However, aripiprazole produced significantly greater improvements in negative and depressive symptoms at weeks 26 and 52 and was associated with significantly lower scores on all EPS assessments compared with haloperidol.

The efficacy of aripiprazole monotherapy in antipsychotic-resistant schizophrenia was evaluated in a 6-week double-blind, randomized trial in patients whose symptoms had not improved during a prospective 4-to 6-week open trial with either olanzapine or risperidone (Kane *et al.* 2007). Subjects were randomly assigned to receive aripiprazole (15-30 mg/day) or perphenazine (8-64 mg/day). After 6 weeks, there was no statistical difference between the two groups on efficacy measures.

A meta-analysis of 14 studies showed no difference in efficacy or safety and tolerability between aripiprazole and brexpiprazole in the treatment of acute schizophrenia in adults (Kishi *et al.* 2020).

The efficacy of aripiprazole in the treatment of schizophrenia in pediatric patients (ages 13-17 years) was evaluated in a 6-week placebo-controlled outpatient trial comparing two fixed daily dosages of aripiprazole (10 mg or 30 mg) with placebo (Findling *et al.* 2008). Both aripiprazole dosages demonstrated statistically significant differences from placebo in reductions in PANSS-Total score; the 30 mg/day dosage was not shown to be more efficacious than the 10 mg/day dosage.

In a 6-week randomized, double-blind dose comparison study, pediatric patients (ages 13-17 years) with schizophrenia were randomly assigned to receive aripiprazole 2, 6-12, or 24-30 mg/day followed by a 52-week open-label extension (Matsumoto *et al.* 2018). Changes in the PANSS-Total score from baseline to endpoint were [?] 19.6 for 2 mg/day, [?] 16.5 for 6-12 mg/day, and [?] 21.6 for 24-30 mg/day. The PANSS-Total score decreased by 7.9 from the open-label extension baseline to week 52.

Efficacy and tolerability of aripiprazole in the maintenance treatment of schizophrenia in pediatric patients (ages 13-17 years) was evaluated in a 52-week double-blind, placebo-controlled, randomized withdrawal design trial (Correll *et al.* 2017). Patients were stabilized on 10-30 mg of oral aripiprazole and then randomly assigned 2:1 to continuation of oral aripiprazole or to placebo. Treatment with aripiprazole was associated with a significantly longer time to exacerbation of psychotic symptoms or relapse compared with placebo ($P = 0.016$).

Two studies have investigated the efficacy of the aripiprazole long-acting depot injection in the prevention of relapse in schizophrenia. In the first investigation, a randomized, placebo-controlled, 52-week multicenter maintenance study, participants requiring long-term treatment with an antipsychotic entered an oral aripiprazole stabilization phase followed by an intramuscular depot conversion and stabilization phase. Patients meeting stabilization criteria for 12 consecutive weeks were then randomly assigned to receive aripiprazole 400 mg long-acting depot or placebo depot for the 52-week double-blind maintenance phase of the study. The primary outcome measure was time to relapse, defined as meeting any or all of the following criteria at any time during the maintenance phase: clinical worsening (defined as Clinical Global Impression-Improvement [CGI-I] score [?] 5 plus increase in any core PANSS item), hospitalization, risk of suicide, or violent behavior. The aripiprazole group had a significantly delayed time to relapse ($P < 0.0001$) and showed a significantly lower rate of relapse compared with the placebo group (9.6% vs. 36.8%, respectively) (Kane *et al.* 2012). The second investigation was a 38-week double-blind noninferiority study that compared relapse rates for aripiprazole once-monthly 400-mg depot injection, oral aripiprazole (10-30 mg/day), and aripiprazole once-monthly 50-mg depot injection, with criteria similar to those used in the Kane *et al.* (2012) study (discussed above). There were no significant differences in rates of relapse between the once-monthly 400-mg depot formulation (7.12%) and the 10-30 mg/day oral formulation (7.76%), and both were significantly superior to the 50-mg depot formulation (21.8%; $P < 0.0001$) (Fleischhacker *et al.* 2014).

One 12-week randomized, double-blind, placebo-controlled Phase III multicenter trial evaluated the efficacy of the aripiprazole once-monthly injection for the management of acute exacerbations in chronic schizophrenia. Patients were randomly assigned to either the aripiprazole once-monthly 400-mg injection group with concomitant oral aripiprazole (mean daily dosage 12.8 mg) for 2 weeks ($n = 168$) or the placebo group ($n = 172$). The aripiprazole group showed sustained improvements in PANSS-Total scores, PANSS-Positive and -Negative subscale scores, and CGI-I scores, with improvements apparent within the first week of administration (Kane *et al.* 2014).

An open-label mirror-image multicenter study in a naturalistic community setting (Kane *et al.* 2013) compared total psychiatric hospitalization rates in 183 patients (18-65 years) who had previously been treated with oral antipsychotics (retrospective phase) and who were then switched to the aripiprazole once-monthly depot formulation for 6 months (prospective phase). The rate of hospitalization for the 6-month prospective phase (14.2%) was found to be lower than the rate for the 6-month retrospective oral antipsychotic period (41.5%; $P < 0.0001$).

Meltzer *et al.* (2015) conducted a 12-week double-blind, placebo-controlled multicenter study comparing once-monthly administration of aripiprazole lauroxil 441 mg or 882 mg versus placebo for 12 weeks. Statistically significant improvement was observed on the PANSS-Total score from baseline to day 85 in both medication groups, with placebo-adjusted differences of [?] 10.9 ($P < 0.001$) and [?] 11.9 ($P < 0.001$) for aripiprazole lauroxil 441 mg and 882 mg, respectively.

The efficacy of the aripiprazole lauroxil 2-month injection with 1-day initiation was evaluated against paliperidone palmitate injection in a 25-

week double-blind study of adult patients with acute exacerbations of schizophrenia in an inpatient setting (Weiden *et al.* 2020). Patients were randomly assigned to receive paliperidone palmitate (234 mg on day 1, 156 mg on day 8, and then 156 mg q 4 weeks) or aripiprazole (aripiprazole lauroxil NanoCrystal Dispersion + oral aripiprazole 30 mg on day 1, aripiprazole lauroxil 1,064 mg on day 8, and then 1,064 mg q 8 weeks) for 25 weeks. For the aripiprazole lauroxil group, the PANSS-Total score was significantly reduced from baseline at weeks 4 ([?] 17.4; $P < 0.001$), 9 ([?] 19.8), and 25 ([?] 23.3). Paliperidone palmitate also had similar reductions in the PANSS-Total score.

Bipolar Disorder

The efficacy of aripiprazole in the treatment of acute manic episodes was established in two 3-week placebo-controlled trials of hospitalized patients whose symptoms met DSM-IV (American Psychiatric Association 1994) criteria for bipolar I disorder with manic or mixed episodes (Keck *et al.* 2003; Sachs *et al.* 2006). Aripiprazole was superior to placebo in reducing the Young Mania Rating Scale (YMRS) total score and the Clinical Global Impression-Bipolar (CGI-BP) Severity of Illness score. In a third large randomized, double-blind trial (Vieta *et al.* 2005), aripiprazole was compared with haloperidol in the treatment of acute bipolar mania over a 12-week period. Significantly more patients remained in treatment and were classified as responders (50% reduction in YMRS score from baseline) at week 12 in the aripiprazole group (49.7%) than in the haloperidol group (28.4%). EPS adverse events were more frequent with haloperidol than with aripiprazole (62.7% vs. 24.0%).

The efficacy of adjunctive aripiprazole with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in a 6-week placebo-controlled study with a 2-week lead-in mood stabilizer monotherapy phase in adult patients who met DSM-IV criteria for bipolar I disorder (Vieta *et al.* 2008). Adjunctive aripiprazole starting at 15 mg/day with concomitant lithium or valproate (in a therapeutic range of 0.6-1.0 mEq/L or 50-125 g/mL, respectively) was found to be superior to lithium or valproate with adjunctive placebo on the basis of reductions in YMRS total scores and CGI-BP Severity of Illness scores.

Aripiprazole monotherapy was evaluated in the treatment of nonpsychotic depressive episodes associated with bipolar I disorder. The results of two identically designed 8-week randomized, double-blind, placebo-controlled multicenter studies were reported by Thase *et al.* (2008). The primary outcome measure was mean change from baseline to week 8 on the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Although statistically significant differences were observed during weeks 1-6, there were no significant differences in change in MADRS total score between aripiprazole and placebo at week 8 in either study.

To evaluate the long-term effectiveness of aripiprazole in delaying relapse in bipolar I disorder, a trial was conducted of patients whose symptoms met DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode (Keck *et al.* 2006). Patients whose condition had been stabilized while taking open-label aripiprazole and who had maintained a clinical response for at least 6 weeks were randomly assigned to receive either aripiprazole or placebo for the 26-week double-blind phase. Aripiprazole-treated patients had significantly fewer relapses than did placebo-treated patients (25% vs. 43%). Aripiprazole was superior to placebo in delaying the time to manic relapse but did not differ from placebo in delaying time to depressive relapse.

The efficacy of the aripiprazole long-acting depot injection in the maintenance treatment of bipolar I disorder was evaluated in a 52-week double-blind, placebo-controlled withdrawal phase study of patients stabilized on oral aripiprazole and transitioned to either 400 mg of the long-acting depot injection or placebo injection (Calabrese *et al.* 2018). The aripiprazole once-monthly injection significantly increased time to hospitalization for any mood episode compared with placebo ($P = 0.0002$), with recurrence rates of 2.3% and 13.5%, respectively.

The efficacy of aripiprazole in the treatment of bipolar I disorder in pediatric patients (ages 10-17 years) was evaluated in two studies. The first study was a 4-week double-blind, placebo-controlled trial of outpatients whose symptoms met DSM-IV criteria for bipolar I disorder manic or mixed episodes with or without psychotic features. The trial compared two fixed daily dosages of aripiprazole (10 mg or 30 mg). Both dosages of aripiprazole were superior to placebo as measured by change from baseline to week 4 on the YMRS total score (Otsuka Pharmaceutical 2020a). The second study was a 30-week randomized, placebo-controlled study of 210 patients (ages 10-17 years) with bipolar I disorder (manic or mixed) with or without psychotic features who were randomly assigned to receive oral aripiprazole 10 mg/day, oral aripiprazole 30 mg/day, or placebo. Both dosages of aripiprazole were superior to placebo; at week 30, aripiprazole-treated patients demonstrated significantly greater improvement in YMRS total scores compared with placebo-treated patients (Findling *et al.* 2013).

Adjunctive Treatment of Major Depressive Disorder

The efficacy of aripiprazole in the adjunctive treatment of MDD was demonstrated in four short-term (6-week) placebo-controlled trials (Berman *et al.* 2007, 2009; Kamijima *et al.* 2018; Marcus *et al.* 2008). During the prospective antidepressant treatment period, patients received one of several antidepressants (escitalopram, fluoxetine, paroxetine controlled release, sertraline, or venlafaxine extended release), each with a single-blind adjunctive placebo. Patients with incomplete response continued taking the antidepressant and were randomly assigned to receive double-blind adjunctive placebo or adjunctive aripiprazole (2-15 mg/day with the potent CYP2D6 inhibitor fluoxetine or paroxetine; 2-20 mg/day with all other antidepressants). In all three trials, the mean change in MADRS total score was significantly greater with adjunctive aripiprazole than with adjunctive placebo. Akathisia and restlessness were significantly more common with adjunctive aripiprazole than with adjunctive placebo.

Fava *et al.* (2012) evaluated the efficacy of low-dosage aripiprazole added to antidepressant therapy for individuals with MDD who had experienced an inadequate response to prior antidepressant treatment. A total of 225 patients were randomly assigned

to receive adjunctive treatment with aripiprazole 2 mg/day or placebo. The pooled, weighted response difference between aripiprazole 2 mg/day and placebo was 5.6% (*P* = 0.18; not significant); the difference on the MADRS was 1.51 (*P* = 0.065; not significant). Of note, there was no difference in rates of akathisia with low-dosage aripiprazole compared with placebo. Thus, a reasonable initial therapeutic approach may be to try a low-dosage (2 mg/day) augmentation of aripiprazole, in view of its better tolerability, and to increase the dosage to 5 mg/day, and if necessary to 10 or 15 mg/day, in the face of continued nonresponse, given that the efficacy of the higher dosage range was supported by robust evidence in three previous positive studies (Fava *et al.* 2012).

In a 36-week multisite study of 1,522 patients with MDD treated at 35 U.S. Veterans Health Administration medical centers, the efficacy of aripiprazole augmentation was evaluated in the treatment of patients unresponsive to at least one antidepressant (Mohamed *et al.* 2017). Patients were randomly assigned to receive adjunctive aripiprazole (2-15 mg), switch to bupropion, or augment with bupropion, with a primary outcome of remission as measured by the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated score. After the acute treatment phase of 12 weeks, remission rates were 22.3% for the switch group, 26.9% for the bupropion augmentation group, and 28.9% for the aripiprazole augmentation group. The aripiprazole augmentation group was significantly more likely to remit than the switch group (*P* = 0.02).

Irritability in Autism Spectrum Disorder

The efficacy of aripiprazole in the treatment of irritability associated with DSM-IV autistic disorder was established in two 8-week placebo-controlled trials of children and adolescents (ages 6-17 years). Efficacy was evaluated with two assessment scales: the Aberrant Behavior Checklist (ABC) and the CGI-I scale. In the first trial (Owen *et al.* 2009), pediatric patients with DSM-IV autistic disorder received aripiprazole (2-15 mg/day, based on clinical response) or placebo. Patients who received aripiprazole (at a mean daily dosage of 8.6 mg at the end of the 8-week treatment) demonstrated significantly improved scores on the ABC-Irritability (ABCI) subscale and on the CGI-I scale compared with patients who received placebo. In the other trial (Marcus *et al.* 2009), three fixed dosages of aripiprazole (5, 10, or 15 mg/day) were compared with placebo. All three dosages of aripiprazole were associated with significantly greater improvement in scores on the ABC-I subscale compared with placebo.

The efficacy and safety of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with DSM-IV autistic disorder were evaluated in a double-blind, randomized, placebo-controlled multicenter study of patients ages 6-17 years. After an initial phase in which single-blind aripiprazole was flexibly dosed (2-15 mg/day; average dosage of 9.0 mg/day) for 13-26 weeks to establish a stable response (defined as a 25% decrease on the ABC-I subscale and a rating of "much improved" or "very much improved" on the CGI-I scale), patients were randomly assigned to receive either aripiprazole (*n* = 41; 2-15 mg/day) or placebo (*n* = 44) for 16 weeks or until relapse. The primary outcome measure was time from randomization to relapse. No statistically significant differences in time to relapse were seen between the drug and the placebo group (*P* = 0.97; hazard ratio, 0.57; number needed to treat, 6) (Findling *et al.* 2014).

Tourette's Disorder

The efficacy of aripiprazole for children and adolescents with Tourette's disorder was established in two short-term trials. In the first study, a double-blind, randomized, placebo-controlled, flexible-dose multicenter trial, patients with Tourette's disorder (*n* = 61) ages 6-18 years were randomly assigned to receive either placebo or aripiprazole (2-20 mg/day) for 10 weeks. Aripiprazole-treated patients demonstrated significantly greater reductions in Yale Global Tic Severity Scale scores compared with patients receiving placebo ([?] 15.0 [8.4] and [?] 9.6 [8.8], respectively; *P* = 0.0196) (Yoo *et al.* 2013). The mean change in phonic tic scores favored the aripiprazole group, but there was no difference in motor tic scores. Treatment-emergent adverse events were not statistically significantly different. The mean dosage was 11.0 mg/day (Yoo *et al.* 2013). In the second study, a Phase III randomized, double-blind, placebo-controlled multicenter trial in patients with a diagnosis of Tourette's disorder (ages 7-17 years), patients first underwent a 3-to 42-day washout period (Sallee *et* *al.* 2017). A total of 133 patients were then randomly assigned to receive low-dosage aripiprazole (5 mg/day if < 50 kg, 10 mg/day if [?] 50 kg), high-dosage aripiprazole (10 mg/day if < 50 kg, 20 mg/day if [?] 50 kg), or placebo for 8 weeks. Both the low-dosage and high-dosage aripiprazole groups showed significant improvement in Yale Global Tic Severity Scale and CGI-Tourette's Syndrome Scale scores compared with the placebo group (Sallee *et al.* 2017).

Off-Label Use

De Deyn *et al.* (2005) compared the efficacy, safety, and tolerability of aripiprazole versus placebo in patients with psychosis associated with Alzheimer's disease in a 10-week double-blind multicenter study. The initial aripiprazole dosage of 2 mg/day was titrated upward (to 5, 10, or 15 mg/day) according to efficacy and tolerability; evaluations included the Neuropsychiatric Inventory (NPI) Psychosis subscale and the BPRS. Aripiprazole-treated patients showed significantly greater improvements from baseline in BPRS-Psychosis subscale and BPRS-Core subscale scores at endpoint compared with patients receiving placebo.

In another double-blind multicenter study (Mintzer *et al.* 2007), patients with psychosis associated with Alzheimer's disease were randomly assigned to receive either placebo or aripiprazole 2, 5, or 10 mg/day. The primary efficacy measure was mean change from baseline to week 10 on the Neuropsychiatric Inventory-Nursing Home (NPI-NH) Psychosis subscale score. Aripiprazole 10 mg/day showed significantly greater improvements than placebo on all efficacy measures (NPI-NH Psychosis subscale, CGI-Severity, BPRS Total and Core, and Cohen-Mansfield Agitation Inventory scores). Aripiprazole 5 mg/day showed significant improvements compared with placebo on BPRS and Cohen-Mansfield Agitation Inventory scores. Aripiprazole 2 mg/day was not efficacious. No antipsychotic is currently approved in the United States for treating the behavioral and psychotic symptoms that often accompany dementia, and all antipsychotics carry a bolded warning based on increased mortality observed in older patients with dementia-related psychosis treated with these agents.

In a 12-week double-blind study (Findling *et al.* 2017), pediatric patients (ages 5-17) with high genetic risk for bipolar disorder and subclinical symptoms of elevated or irritable mood (cyclotaxia) were randomly assigned to receive oral aripiprazole or placebo. Aripiprazole was superior to placebo in reduction from baseline of YMRS total scores ($P < 0.005$).

Nickel *et al.* (2006) conducted a double-blind, placebo-controlled study in patients whose clinical presentation met DSM-III-R (American Psychiatric Association 1987) criteria for borderline personality disorder. Subjects were randomly assigned in a 1:1 ratio to receive either aripiprazole (15 mg/day) or placebo for 8 weeks. At endpoint, significant changes in scores on most scales of the Symptom Checklist-90 Revised, on the Hamilton Rating Scale for Depression (Ham-D), on the Hamilton Anxiety Scale (Ham-A), and on all subscales of the State-Trait Anger Expression Inventory were observed in subjects who received aripiprazole. The improvements observed at 8 weeks were maintained at 18-month follow-up (Nickel *et al.* 2007).

Tiihonen *et al.* (2007) conducted a study in which patients whose symptoms met DSM-IV criteria for intravenous amphetamine dependence were randomly assigned to receive aripiprazole (15 mg/day), slow-release methylphenidate (54 mg/day), or placebo for 20 weeks. The study was terminated prematurely because of unexpected results in the interim analysis. Contrary to the hypothesized result, patients who received aripiprazole treatment had significantly more amphetamine-positive urine samples than did patients in the placebo group, and patients who received methylphenidate had significantly fewer amphetamine-positive urine samples than patients who received placebo.

The efficacy of aripiprazole in the treatment of schizophrenia comorbid with active cocaine dependence was evaluated in an 8-week double-blind study (Beresford *et al.* 2017). Patients ($N = 44$) were randomly assigned to receive either aripiprazole (15-30 mg/day) or perphenazine (4-8 mg doses given three times/day), with a primary outcome of cocaine-free urine samples and a secondary outcome of reductions in craving scores. Cocaine-free urine samples did not differ between groups. Cravings, in respect to intensity, frequency, and duration, were seen to decrease in the aripiprazole group by week 6 but did not correlate with reduced cocaine use by study endpoint.

In a 12-week double-blind, placebo-controlled multicenter trial (Anton *et al.* 2008) evaluating the efficacy of aripiprazole for patients with DSM-IV alcohol dependence, aripiprazole did not differ from placebo on the study's primary efficacy measure, mean percentage of days abstinent.

The efficacy of aripiprazole (up to 15 mg/day) and topiramate in reducing alcohol-related outcomes was evaluated in a 5-week double-blind, placebo controlled, between-subject human laboratory study (Haass-Koffler *et al.* 2018). Aripiprazole did not result in significant changes in alcohol use or cravings.

Brexpiprazole

Brexpiprazole is currently approved in the United States for schizophrenia in both adults and pediatric patients ages 13-17 years and for use as an adjunct to antidepressant treatment for adults with MDD who have had an inadequate response to antidepressant therapy (Otsuka Pharmaceutical 2023). In 2023, brexpiprazole became the first pharmacological agent to receive FDA approval for treatment of agitation associated with dementia due to Alzheimer's disease (Otsuka Pharmaceutical 2023).

Schizophrenia

The efficacy of brexpiprazole in the treatment of acute symptom exacerbations in schizophrenia has been evaluated in multiple studies, including two 6-week double-blind, placebo-controlled multicenter trials. In the BEACON Phase III multicenter

study, patients with acute schizophrenia were randomly assigned to receive aripiprazole (1, 2, or 4 mg/day) or placebo. Brexpiprazole 4 mg/day produced statistically significant reductions ([?] 6.47; *P* = 0.0022) compared with placebo in the PANSS-Total score (Kane *et al.* 2015). In another 6-week multicenter double-blind, placebo-controlled Phase III trial (VECTOR study), patients with schizophrenia experiencing an acute exacerbation were randomly assigned to receive brexpiprazole (0.25, 2, or 4 mg/day) or placebo. At 6 weeks, both the 2 mg/day and the 4 mg/day dosages of brexpiprazole had produced statistically significantly greater reductions ([?] 8.72 [$P < 0.0001$] and [?] 7.64 [$P = 0.0006$] for 2 mg/day and 4 mg/day, respectively) in PANSS-Total scores compared with placebo (Correll *et al.* 2015).

A Phase III 52-week maintenance study was conducted to demonstrate the effectiveness of brexpiprazole in preventing exacerbation or relapse of psychosis in patients with schizophrenia. Patients with acute exacerbation of psychotic symptoms were started on brexpiprazole (flexible dosing) over 1-4 weeks. Those who met the stability criteria for 12 weeks were randomly assigned to double-blind maintenance treatment with brexpiprazole or placebo for up to 52 weeks. The time to impending relapse was significantly delayed with brexpiprazole treatment compared with placebo (Fleischhacker *et al.* 2017). A similar result for tolerability and efficacy was replicated in another Phase III randomized, double-blind, placebo-controlled study over the course of 52 weeks (Forbes *et al.* 2018).

There are limited head-to-head studies comparing brexpiprazole with other antipsychotics. An exploratory, open-label study was conducted to evaluate the effects of brexpiprazole and aripiprazole. Patients with acute exacerbation of schizophrenia were randomly assigned to brexpiprazole (3 mg/day target dose) and aripiprazole (15 mg/day target dose). Results showed a clinically relevant improvement in psychopathology and a reduction in the PANSS-Total scores in both brexpiprazole and aripiprazole treatment groups ([?] 22.9 and [?] 19.4, respectively; $P < 0.0001$) (Citrome *et al.* 2016). Additionally, the study found that brexpiprazole had a lower incidence of akathisia (9.4%) compared with that of aripiprazole (21.2%) (Citrome *et al.* 2016). The comparable response rate of aripiprazole and brexpiprazole was also supported by findings in recent meta-analyses (Huhn *et al.* 2019; Kishi *et al.* 2020). In the meta-analysis comparing brexpiprazole and aripiprazole, the ranked probability results showed that brexpiprazole had a lower incidence of side effects and a better risk-benefit ratio than aripiprazole in the treatment of patients with acute schizophrenia (Kishi *et al.* 2020). Brexpiprazole was also compared with quetiapine in a large, double-blind, placebo-controlled trial (LIGHTHOUSE study), where both were found to produce a clinically relevant reduction in PANSS-Total score; however, brexpiprazole failed to reach statistical significance compared with placebo, possibly because of an unexpectedly high placebo response (Frampton 2019).

Adjunctive Treatment of Major Depressive Disorder

The antidepressant effect of brexpiprazole may be attributable to its 5-HT$_{1A}$ and D$_2$ partial agonism and 5-HT$_7$ and a$_2$ antagonism, but the exact mechanism remains unknown. The efficacy of brexpiprazole in the adjunctive treatment of MDD has been demonstrated in two pivotal randomized, double-blind Phase III studies. In the first study (Thase *et al.* 2015a), patients who had not responded to three prior trials with antidepressants entered an 8-week prospective period of open-label treatment with an antidepressant. Patients who showed inadequate response (defined as a score of [?] 14 on the 17-item Ham-D, < 50% reduction from baseline in Ham-D and MADRS total scores, and a CGI-I score of [?] 3) were randomly assigned to receive double-blind antidepressant plus brexpiprazole (2 mg/day) or antidepressant plus placebo. Adjunctive brexpiprazole 2 mg/day produced statistically significant reductions in MADRS total scores compared with adjunctive placebo ([?] 8.36 vs. [?] 5.15, respectively; $P = 0.0002$) (Thase *et al.* 2015a).

The second study (Thase *et al.* 2015b) also evaluated the efficacy and safety of brexpiprazole (1 mg and 3 mg/day) versus placebo in the adjunctive treatment of antidepressant-resistant MDD. The study also included an 8-week single-blind prospective treatment phase in which patients received one antidepressant. Patients who had an inadequate response (defined as a Ham-D score [?] 14, < 50% reduction from baseline in Ham-D and MADRS total scores, and a CGI score [?] 3) were randomly assigned to receive double-blind antidepressant plus brexpiprazole (1 mg/day or 3 mg/day) or antidepressant plus placebo. The brexpiprazole 3 mg/day treatment group showed statistically significantly greater improvement (assessed by mean reduction from baseline in MADRS total score) compared with the placebo group ([?] 8.29 vs. [?] 6.33, respectively; $P = 0.0079$), whereas the numerical improvement in MADRS total score was not statistically significantly greater for brexpiprazole 1 mg/day versus placebo ([?] 7.64; $P = 0.0079$) (Thase *et al.* 2015b).

Additional studies and reviews have examined the efficacy of brexpiprazole as an augmentation agent for MDD, yielding some mixed results. Yoon *et al.* (2017) conducted a meta-analytic study to evaluate the use of brexpiprazole in randomized controlled trials involving patients with MDD. Findings showed that brexpiprazole had greater mean differences in the score changes for the MADRS ([?] 1.76; $P < 0.00001$) and the Ham-D ([?] 1.21; $P < 0.00001$) compared with placebo, especially at higher dosages (1-3 mg/day). In the same study, the meta-analysis of negative studies also yielded positive results in MADRS score reductions ([?] 1.19; $P = 0.03$) and Ham-D score reductions ([?] 0.76; $P = 0.03$) compared with placebo. Additionally, the study showed a higher frequency of responders ([?] 50% reduction in MADRS score) and remitters (MADRS score [?] 10 with [?] 50% reduction) with brexpiprazole use, with risk ratios of 1.57 ($P < 0.00001$) and 1.55 ($P = 0.0004$), respectively (Yoon *et al.* 2017). Head-to-head studies comparing the efficacy of adjunctive brexpiprazole against that of other adjunctive atypical antipsychotics remain limited, but the overall efficacy appears to be comparable at this time.

Agitation Associated With Dementia due to Alzheimer's Disease

Two Phase III randomized, double-blind, placebo-controlled, fixed-dose studies were conducted to establish the efficacy of brexpiprazole in the treatment of agitation associated with dementia due to Alzheimer's disease (Otsuka Pharmaceutical 2023). Both studies required participants to have a diagnosis of probable Alzheimer's disease, a Mini-Mental State Examination (MMSE) score of [?] 5 and [?] 22, and sufficient agitated behavior(s) to warrant use of pharmacotherapy. The Cohen-Mansfield Agitation Inventory (CMAI) total score was used to measure the frequency of agitated behavior, with the primary endpoint focused on change between baseline and week 12 of participation. Participant ages ranged from 51 to 90 years.

In the first Phase III study, participants were randomly assigned to one of three groups: placebo, oral dosage of 1 mg/day, and oral dosage of 2 mg/day. Both medication groups were started at a dosage of 0.25 mg once daily, which was titrated over the course of the study to the respective assigned dosage goals. At the completion of the 12-week trial, the 2 mg/day group demonstrated statistically significantly greater improvement in the CMAI total score in comparison with the placebo group, with an adjusted mean difference of -3.8 (*P* = 0.04) (Grossberg *et al.* 2020).

In the second Phase III study, participants were randomly assigned to one of three groups: placebo, oral dosage of 2 mg/day, and oral dosage of 3 mg/day. Both medication groups were started at 0.5 mg once daily, with the dosage increased over the course of the study period to the respective assigned dosage goals. At the completion of the 12-week trial, the 2 mg/day and 3 mg/day groups showed improved total CMAI scores in comparison with the placebo group, with an adjusted mean difference of -5.3 (Otsuka Pharmaceutical 2023).

Two Phase III clinical trials showed the efficacy of brexpiprazole 2 mg/day (flexible and fixed dosing) for the treatment of agitation in patients with Alzheimer's disease. The studies also demonstrated an improved tolerability and safety profile for brexpiprazole in comparison with the currently available second-generation antipsychotics (Caraci *et al.* 2020; Grossberg *et al.* 2020). It is important to note that these two trials excluded patients with a history of stroke or vascular dementia. Also of note, antipsychotics are not FDA approved for the treatment of behavioral problems associated with dementia because of the black box warning of an increased risk of mortality in this population (Otsuka Pharmaceutical 2023).

These Phase III studies demonstrated brexpiprazole's improved tolerability and safety (supported by use of a slow titration schedule) in comparison with the other available second-generation antipsychotics in the treatment of agitation in patients with Alzheimer's disease (Caraci *et al.* 2020). However, brexpiprazole is not indicated as a prn (as needed) treatment for agitation in patients with Alzheimer's disease (Otsuka

Pharmaceutical 2023). Additionally, antipsychotics are not FDA approved for the treatment of behavioral problems associated with dementia because of the black box warning for an increased risk of mortality in this population (Otsuka Pharmaceutical 2023).

Off-Label Use

Brexpiprazole has a higher affinity for serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors, which may help it exert an anxiolytic effect in addition to antidepressant effects (Yoon *et al.* 2017). In the post hoc analyses of three placebo-controlled studies in adults with MDD and inadequate response to antidepressants, adjunctive brexpiprazole dosages (2 mg and 3 mg/day) have been shown to significantly reduce the total Ham-A score (Thase *et al.* 2018). Of note, the benefits were seen in the subgroups of depressed patients with anxious distress, who may be less likely to respond to antidepressant monotherapy. Therefore, brexpiprazole may offer another potential option for individuals struggling with depressive symptoms for which anxiety is part of the presentation.

Side Effects and Toxicology

Aripiprazole

A pooled analysis of safety and tolerability data from the five short-term studies (Marder *et al.* 2003; Stock *et al.* 2002) showed that aripiprazole treatment was well tolerated.

The most commonly reported adverse events with aripiprazole were headache, insomnia, agitation, and anxiety, which were similar in the aripiprazole and placebo groups. The adverse-event profile of aripiprazole did not vary according to patient characteristics of age, sex, and race or ethnicity, and no deaths were reported during the short-term studies. Data from four fixed-dosage studies (Bristol Myers Squibb 2001; Cutler *et al.* 2006; Kane *et al.* 2002; Potkin *et al.* 2003) showed that somnolence was the only adverse event seen with aripiprazole that was possibly dose related. Objective rating scale assessments were used to measure changes in parkinsonian symptoms (Simpson-Angus Scale [SAS]), dyskinesias (Abnormal Involuntary Movement Scale), and akathisia (Barnes Akathisia Rating Scale [BARS]). SAS scores with aripiprazole did not differ significantly from those with placebo, whereas Abnormal Involuntary Movement Scale scores improved significantly from baseline with aripiprazole compared with placebo. Aripiprazole did not produce consistent dose-dependent changes in BARS scores.

According to the FDA-approved package insert, treatment-emergent adverse events most commonly reported with aripiprazole (occurring in 10% of patients with an incidence greater than that with placebo) in short-term trials of patients with schizophrenia (up to 6 weeks) or bipolar disorder (up to 3 weeks), respectively, included headache (aripiprazole 30% vs. placebo 25%), anxiety (20% vs. 17%), insomnia (19% vs. 14%), nausea (16% vs. 12%), vomiting (12% vs. 6%), dizziness (11% vs. 8%), constipation (11% vs. 7%), dyspepsia (10% vs. 8%), and akathisia (10% vs. 4%) (Otsuka Pharmaceutical 2020a).

The most common adverse events reported for the aripiprazole long-acting injectable formulation in the Kane *et al.* (2012) 52-week trial were insomnia (aripiprazole 10% vs. placebo 9%), tremor (5.9% vs. 1.5%), headache (5.9% vs. 5.2%), and akathisia (5.6% vs. 6%). In the Kane *et al.* (2014) 12-week acute management of schizophrenia study, the most common adverse events were weight gain (aripiprazole 16.8% vs. placebo 7%), headache (14.4% vs. 16.3%), and akathisia (11.4% vs. 3.5%). There was no significant difference in rates of EPS other than akathisia between the 400-mg aripiprazole group and the placebo group. In a 24-week open-label parallel-arm study conducted by Mallikaarjun *et al.* (2013), the tolerability and safety of aripiprazole once monthly in schizophrenia were comparatively evaluated for dosages of 200 mg, 300 mg, and 400 mg. The most common adverse events were injection-site pain (aripiprazole 400 mg, 28.6%), tremor (aripiprazole 300 mg, 6.7%; aripiprazole 400 mg, 21.4%), and vomiting (aripiprazole 300 mg, 13.3%; aripiprazole 400 mg, 14.3%).

The most common adverse events in a 12-week Phase III trial of aripiprazole lauroxil in the treatment of acute exacerbations of schizophrenia were akathisia, headache, insomnia, and injection-site pain (occurring in 5% of patients). Akathisia occurred at twice the rate of placebo for aripiprazole lauroxil 882 mg and 441 mg (4.3%, 11.6%, and 11.5%, respectively) (Meltzer *et al.* 2015). The majority (> 75%) of akathisia episodes occurred within 3 weeks of receiving the first injection. In a 52-week safety study (Nasrallah *et al.* 2019) of patients with schizophrenia taking aripiprazole lauroxil, weight gain was minimal (0.8 kg), with no statistically significant changes in metabolic parameters at the end of the study period.

Minimal changes in mean body weight were observed with aripiprazole treatment in short-term studies (pooled data, 0.71 kg) (Marder *et al.* 2003) and in long-term studies (26-week, [?] 1.26 kg; 52-week, + 1.05 kg) (Kasper *et al.* 2003; Pigott *et al.* 2003).

Olanzapine and aripiprazole were compared on their propensity to cause weight gain and other metabolic disturbances in a 26-week randomized, double-blind multicenter trial (McQuade *et al.* 2004). Statistically significant differences in mean weight change between treatments were observed beginning at week 1 and were sustained throughout the study. At week 26, there was a mean weight loss of 1.37 kg (3.04 lb) with aripiprazole compared with a mean weight gain of 4.23 kg (9.40 lb) with olanzapine among patients who continued therapy ($P < 0.001$). Changes in fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were significantly different in the two treatment groups, with worsening of the lipid profile among patients treated with olanzapine.

Aripiprazole treatment was not associated with increases in prolactin levels during either short-or long-term studies. In fact, prolactin levels have been shown to be slightly decreased by aripiprazole (Crespo-Facorro *et al.* 2017).

Overall, aripiprazole treatment is associated with a low incidence of EPS (other than akathisia) and EPS-related symptoms and with minimal or no effects on weight gain, QTc interval, or circulating levels of cholesterol, glucose, and prolactin. Treatment with aripiprazole may reduce the burden of antipsychotic-associated side effects, leading to improved patient adherence and decreased risks of acute relapse.

Brexpiprazole

Overall, brexpiprazole has been well tolerated in the four short-term clinical trials conducted thus far, with lower rates of discontinuation due to adverse events compared with placebo (Citrome 2015). In pooled analyses of brexpiprazole in the adjunctive treatment of MDD, the rate of discontinuation due to adverse reactions for all dosages of brexpiprazole was 3%, compared with 1% for placebo (Otsuka Pharmaceutical 2023). In the two Phase III trials of brexpiprazole in acute schizophrenia, the overall rates of discontinuation due to adverse events for brexpiprazole were lower than those for placebo (Correll *et al.* 2015; Kane *et al.* 2015).

The most common side effects varied among available studies. In one Phase III trial in acute schizophrenia, the most common adverse events for brexpiprazole were headache, agitation, and insomnia, with rates of akathisia lower than those with placebo but with a dose-dependent increase for brexpiprazole (Kane *et al.* 2015). Comparatively, the most common adverse event in another Phase III trial was akathisia for brexpiprazole 2 mg (4.4%) and 4 mg (7.2%) versus placebo (2.2%), with akathisia most commonly occurring within the first 3 weeks of treatment (Correll *et al.* 2015). Akathisia is more likely at dosages above 4 mg/day (Kane *et al.* 2016), but the incidence of akathisia for brexpiprazole (9.5%) is still lower than that for aripiprazole (21.2%) (Citrome *et al.* 2016), probably because of brexpiprazole's stronger 5-HT_{2A} antagonism (Correll *et al.* 2016).

Brexpiprazole has a lower incidence of sedation and somnolence due to its low affinity for receptors associated with sedation (e.g., H_1) (Correll *et al.* 2016). It has also not been found to have a significant impact on QTc (McEvoy and Citrome 2016). Pooled data from two short-term Phase III schizophrenia trials showed that 10% of brexpiprazole-treated patients had weight gains of [?] 7% from baseline during a 6-week trial, compared with 4.1% of patients receiving placebo (Citrome 2015; Otsuka Pharmaceutical 2023). Similarly, the pooled data from both short-term MDD trials showed weight gain in the brexpiprazole group to be higher than that in the placebo group (6.7% vs. 1.9%), with the greatest increase being 1.6 kg for brexpiprazole 3 mg/day at 6 weeks (Citrome 2015; Otsuka Pharmaceutical 2023). Although most antipsychotics have been associated with chronic elevated risk of metabolic changes, brexpiprazole is less likely to affect triglyceride concentrations and may be associated with better metabolic outcomes (Pillinger *et al.* 2020), although moderate weight gain may be seen in short-and long-term treatment (Newcomer *et al.* 2019).

Change in prolactin level was studied in all treatment trials. In one Phase III trial of brexpiprazole in schizophrenia, there was no statistically significant change in prolactin level (Correll *et al.* 2015). In a second Phase III short-term trial of brexpiprazole in schizophrenia, the incidence of potentially clinically relevant prolactin values (one to two times the upper limit of normal) was highest in the brexpiprazole 4 mg/day group (19.1%) compared with the placebo group (13.9%) (Kane *et al.* 2015). In a short-term Phase III trial of brexpiprazole in the adjunctive treatment of MDD, 0.4% of patients receiving brexpiprazole 3 mg/day, compared with 1.4% of patients receiving placebo, had a prolactin level greater than three times the upper limit of normal (Thase *et al.* 2015a).

The incidence of EPS was evaluated in all four short-term treatment trials by means of the BARS and the SAS (Otsuka Pharmaceutical 2023). The percentage of patients treated with brexpiprazole plus an antidepressant who showed a shift from normal to abnormal was greater compared with placebo for both the BARS (4% vs. 0.6%) and the SAS (4% vs. 3%) (Otsuka Pharmaceutical 2023). Similarly, the brexpiprazole group showed a greater shift from normal to abnormal compared with placebo in both the BARS (2% vs. 1%) and the SAS (7% vs. 5%) in pooled data from both schizophrenia trials (Otsuka Pharmaceutical 2023). Additionally, brexpiprazole was found to have a lower risk of D_2 receptor sensitization after a subacute treatment in an animal study, further suggesting its lower risk of EPS in the long term (Amada *et al.* 2019).

With an overall minimal incidence of EPS beyond akathisia and minimal observed changes in QTc, lipid panel, and glucose panel values compared with placebo, brexpiprazole is another antipsychotic with a tolerable side-effect profile that may improve adherence in the long term (Correll *et al.* 2015; Kane *et al.* 2015; Thase *et al.* 2015a, 2015b).

Drug-Drug Interactions

Aripiprazole

Because aripiprazole is metabolized primarily by the hepatic enzymes CYP2D6 and CYP3A4, it has the potential to interact with other substrates for these enzymes. Inducers of these enzymes may increase clearance and thereby reduce blood levels of aripiprazole, whereas inhibitors of CYP3A4 or CYP2D6 may inhibit elimination and thereby increase blood levels of aripiprazole. In vivo studies showed decreased levels of aripiprazole and dehydroaripiprazole in the plasma when aripiprazole was coadministered with carbamazepine, a CYP3A4 inducer. The aripiprazole dosage should therefore be increased when the drug is administered concomitantly with carbamazepine. Findings from in vivo studies that coadministered aripiprazole with ketoconazole (a CYP3A4 inhibitor) or with quinidine (a CYP2D6 inhibitor) suggest that the aripiprazole dosage should be reduced when aripiprazole is administered with strong CYP3A4 or CYP2D6 inhibitors. Aripiprazole exhibits a_1-adrenergic receptor antagonist activity and therefore may enhance the effects of certain antihypertensive agents (Otsuka Pharmaceutical 2020a).

Brexpiprazole

Brexpiprazole is metabolized primarily by hepatic CYP enzymes 2D6 and 3A4; therefore, coadministration with inducers or inhibitors of these CYP enzymes requires dosage adjustments for brexpiprazole. In vivo studies showed increased levels of brexpiprazole when it was coadministered with ketoconazole (a CYP3A4 inhibitor) or quinidine (a CYP2D6 inhibitor), and it is therefore recommended that brexpiprazole dosages be reduced when brexpiprazole is coadministered with known CYP2D6 and CYP3A4 inhibitors. Plasma levels of brexpiprazole were decreased when the drug was coadministered with rifampin (a CYP3A4 inducer) during in vivo studies, and it is therefore recommended that brexpiprazole dosages be increased when brexpiprazole is coadministered with known CYP3A4 inducers. Brexpiprazole has limited induction or inhibition of other CYP enzymes, according to multiple in vivo studies (Otsuka Pharmaceutical 2023).

Conclusion

Aripiprazole was the first agent that was not a full D_2 receptor antagonist to show rapid and sustained antipsychotic activity, and it may be considered the first partial dopamine agonist combined with 5-HT-stabilizing properties. Short-term and long-term clinical trials in adult and pediatric patients with schizophrenia and bipolar I disorder have demonstrated that aripiprazole combines sustained antipsychotic and mood-stabilizing efficacy with an excellent safety and tolerability profile. Additional augmentation trials have confirmed the utility of aripiprazole in alleviating depressive symptoms for patients with MDD who have not achieved adequate symptom relief with antidepressants alone. The efficacy and safety of aripiprazole have also been established in child and adolescent populations for the management of irritability in autism spectrum disorders and Tourette's disorder. Aripiprazole is now also available in two different long-term depot injectable formulations for the management of schizophrenia in adults.

Brexpiprazole shares multiple traits with aripiprazole, including partial dopamine agonism and 5-HT-stabilizing properties. However, brexpiprazole has lower intrinsic dopaminergic activity than does aripiprazole, which may indicate an even more favorable side-effect profile relative to the well-tolerated older drug. Several short-term clinical trials of adult patients with acute schizophrenia or with a lack of response to previous therapy for MDD have confirmed the efficacy and tolerability of this newly established atypical antipsychotic. A variety of clinical trials with brexpiprazole targeting different treatment populations, including head-to-head trials with other antipsychotics to further establish clinical efficacy, have been initiated or are ongoing.

In general, both aripiprazole and brexpiprazole are associated with low incidences of EPS, QTc interval prolongation, prolactin elevation, weight gain, and disturbance

of glucose or lipid metabolism. The combination of efficacy, safety, and tolerability suggests that both aripiprazole and brexpiprazole are important options for the acute treatment of schizophrenia and for the adjunctive treatment of MDD. Aripiprazole additionally is an important treatment option for bipolar I disorder, irritability in autism spectrum disorder, and Tourette's disorder as well as for long-term management of schizophrenia.

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CHAPTER 31

Ziprasidone and Asenapine

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This chapter reviews background information, pharmacological profiles, clinical indications, adverse events, and other considerations for two atypical, or second-generation, antipsychotic agents, ziprasidone and asenapine. These medications each offer unique potential benefits and overall favorable safety profiles that led to their regulatory approval in the United States and multiple other countries.

Ziprasidone

History and Discovery

Ziprasidone (CP-88059) is an atypical, or second-generation, antipsychotic agent that has activity for treating symptoms of schizophrenia and schizoaffective disorder and for treating mania and mixed states in bipolar disorder, with limited adverse extrapyramidal, sedative, anticholinergic, and cardiometabolic effects. First approved in 2001, this antipsychotic was initially part of a new drug application for the treatment of psychotic disorders submitted to the FDA in 1997. Because of concerns regarding an increase in the mean duration of the QT interval, an electrocardiographic measure of the ventricular depolarization and repolarization phases of cardiac conduction, the application was not initially approved. Further studies, designed in collaboration with the FDA, quantified the limited extent of the QTc interval lengthening effect seen with ziprasidone compared with that seen with other agents in wide use; these studies established the safety of ziprasidone with respect to cardiac conduction and established a benchmark for the approach to evaluating drug effects on the QT interval that has subsequently been applied to other agents evaluated by the FDA. Ziprasidone received regulatory approval in the United States in 2001 and is now available in more than 90 countries. Ziprasidone is currently available as oral capsules (20, 40, 60, and 80 mg) and as an intramuscular injection (20-mg single-dose vial).

Structure-Activity Relations and Pharmacological Profile

Ziprasidone, or 5-{2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl}-6-chloro-1,3-dihydro-2H-indol-2-one, is a novel benzisothiazolyl piperazine antipsychotic (Figure 31-1).

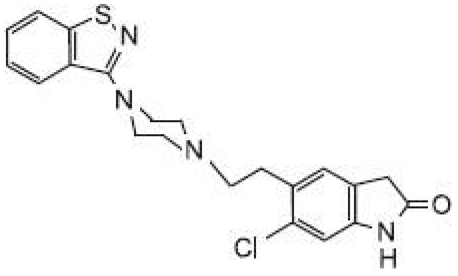

FIGURE 31-1. Chemical structure of ziprasidone.

Ziprasidone is a potent antagonist at dopamine type 2 (D_2) receptors with inverse agonist activity at serotonin type 2A (5-HT_{2A}) receptors. D_2 receptor antagonism is thought to be a key mechanism explaining its efficacy for the treatment of psychotic symptoms (Kapur and Remington 2001); in vivo PET analysis has shown that occupancy of at least 60% of striatal D_2 receptors, predictive of clinical antipsychotic response, is observed at ziprasidone plasma concentrations attained with dosages [?] 120 mg/day (Mamo *et al.* 2004). However, ziprasidone also has inverse agonist activity at 5-HT_{2A} receptors, an effect that can disinhibit dopamine neurotransmission in the nigrostriatal, mesocortical, and tuberoinfundibular pathways (Kapur and Remington 2001; Schmidt *et al.* 2001). This effect suggests a mechanism for reduced liability for extrapyramidal side effects (EPS) compared with antipsychotics with unopposed D_2 receptor antagonism. Ziprasidone's relatively high in vitro 5-HT_{2A}/D_2 receptor affinity ratio, compared with that of many other second-generation antipsychotics (SGAs), predicts a low liability for EPS and potential benefits for negative symptoms (Altar *et al.* 1986).

Ziprasidone exhibits antagonist activity at serotonin type 1D (5-HT_{1D}) and type 2C (5-HT_{2C}) receptors and unusual (among SGAs) agonist activity at serotonin type 1A (5-HT_{1A}) receptors (DeLeon *et al.* 2004; Schmidt *et al.* 2001). Ziprasidone's 5-HT_{1A} affinity is comparable to that of buspirone, an agent with antidepressant and anxiolytic properties (Diaz-Mataix *et al.* 2005; Ichikawa *et al.* 2001; Mazei *et al.* 2002; Millan 2000; Rollema *et al.* 2000; Sumiyoshi *et al.* 2003; Tauscher *et al.* 2002). Potent antagonism at 5-HT_{1D} receptors has been proposed to mediate antidepressant and anxiolytic effects (Briley and Moret 1993; Zorn *et al.* 1998). Blockade of 5-HT_{2C} receptors disinhibits both dopamine and norepinephrine neurons in the cortex, an effect that could contribute to improvements in cognition and affect (Bymaster *et al.* 2002; Mazei *et al.* 2002; Stahl 2003). Although 5-HT_{2C} receptor antagonist activity might predict weight gain liability according to a 5-HT_{2C} knockout mouse model of obesity (Tecott *et al.* 1995), clinically significant predictive effects of 5-HT_{2C} receptor antagonist activity on the relative risk for weight gain associated with antipsychotic drugs have not been reliably detected (Kroeze *et al.* 2003), and the risk for weight gain associated with ziprasidone is observed to be among the lowest of available antipsychotics (Allison *et al.* 1999).

Another important feature of ziprasidone is its relatively high affinity for serotonin and norepinephrine transporters (Seeger *et al.* 1995; Tatsumi *et al.* 1999). In vitro, ziprasidone demonstrates dose-dependent reuptake inhibition of serotonin and norepinephrine transport, with effects ranging up to those of imipramine and amitriptyline (Schmidt *et al.* 2001). In vivo, the clinical significance of ziprasidone's monoaminergic reuptake inhibition may be limited by plasma protein binding or may be clinically relevant only at daily dosages higher than those approved.

Ziprasidone has low affinity for histaminergic type 1 (H_1), muscarinic type 1 (M_1), and a_1-noradrenergic receptors. Among the biogenic amine receptors, H_1 receptor antagonist activity may be the largest predictor of weight gain liability (Kroeze *et al.* 2003). H_1 antagonist activity also predicts sedative effects, which are undesirable for patients aiming to maximize cognitive performance and social, occupational, and community engagement. Low affinity for a_1-adrenergic receptors predicts a lower likelihood of orthostatic hypotension and sedation with ziprasidone than with commonly used antipsychotics with potent a_1-adrenergic receptor antagonist activity. Low affinity for M_1 receptors predicts a low risk for anticholinergic side effects.

Evidence from randomized clinical trials, as well as PET results noted previously, suggests that ziprasidone target dosages should be higher than those originally recommended for schizophrenia. In the United States, it was initially recommended that ziprasidone treatment in patients with schizophrenia be initiated at a dosage of 20 mg bid, with the dosage then titrated at intervals of no less than 2 days to a maximum of 80 mg bid (Pfizer Inc. 2020). In contrast, subsequent FDA approval of ziprasidone for the treatment of bipolar mania included a recommendation that treatment be initiated at 40 mg bid with a more rapid titration; on the second day of treatment, the dosage might be increased to 60 or 80 mg bid, with subsequent adjustment based on tolerability and efficacy within a 40-to 80-mg bid range. Ziprasidone dosages of 120-160 mg/day are observed to be more effective than lower dosages in the treatment of acute schizophrenia

(Kane 2003b) and bipolar disorder in adults (Citrome *et al.* 2009b) and are associated with lower rates of medication discontinuation (Citrome *et al.* 2009c). Reported clinical experience with ziprasidone has suggested the need for dosages greater than 160 mg/day in selected patients (Citrome *et al.* 2009a; Harvey and Bowie 2005; Nemeroff *et al.* 2005). However, a dosage of 320 mg/day, twice the maximal recommended dosage of 160 mg/day, did not lead to any additional symptom improvement in a small 8-week placebo-controlled trial compared with a dosage of 160 mg/day, and plasma drug levels were similar between the two dosages at the end of the study period. There was a trend toward increased diastolic blood pressure, more negative symptoms, and greater QTc prolongation at 320 mg/day (Goff *et al.* 2013).

Pharmacokinetics and Drug-Drug Interactions

On the basis of evidence of enhanced absorption of ziprasidone in the presence of food, it is recommended that oral ziprasidone be taken with meals of at least 500 kcal to avoid a substantial reduction in drug absorption (Gandelman *et al.* 2009) that cannot be effectively compensated for by increasing the dosage (Citrome 2009b). Administration with food increases absorption by more than 50%, giving ziprasidone an oral bioavailability of approximately 60% (Pfizer Inc. 2020). The maximum plasma concentration (C_{max}) is achieved within 3.7-4.7 hours and reaches 45-139 mg/L in healthy volunteers receiving 20-60 mg bid, and steady-state serum concentrations occur within 1-3 days of twice-daily dosing (Hamelin *et al.* 1998; Miceli *et al.* 2000c). In contrast to oral administration, intramuscular administration of ziprasidone results in 100% bioavailability. A therapeutic plasma level is reached within 10 minutes, and C_{max} is achieved within 30 minutes of administration of a 20-mg dose (Pfizer Inc. 2020).

The mean apparent volume of distribution of ziprasidone is 1.5 L/kg (Pfizer Inc. 2020), which is lower than that of many other antipsychotic drugs. Given the greater potential for unwanted interactions with various intracellular targets that has been observed with lipophilic drugs having a high volume of distribution (Dwyer *et al.* 1999), this may be a favorable attribute of ziprasidone and other similar compounds. Ziprasidone is more than 99% bound to plasma proteins.

Pharmacokinetic studies have examined ziprasidone bioavailability under fasting conditions and after the consumption of food with varying caloric and fat compositions to better understand effects of food intake on drug availability (Gandelman *et al.* 2009; Lombardo *et al.* 2007). In an open-label, nonrandomized, six-way crossover study, healthy adults received single doses of ziprasidone under fasting conditions and then under fed conditions with a standard meal of 800-1,000 calories. Dose-proportional increases in ziprasidone area under the curve (AUC) and C_{max} were observed under fed but not fasting conditions. C_{max} was significantly higher in fed states than in fasting states at doses of 40 mg (63% higher) and 80 mg (97% higher). Results from two additional open-label crossover studies further clarified the factors regulating drug bioavailability (Gandelman *et al.* 2009; Lombardo *et al.* 2007). They indicated that 1) medium-calorie meals (500 calories) are associated with ziprasidone exposure close to the exposure that can be achieved with high-calorie meals (1,000 calories) and nearly twice the exposure observed under fasting conditions, and 2) absorption is not significantly influenced by the fat content of the meal.

Ziprasidone is extensively metabolized, with a mean terminal elimination half-life of approximately 7 hours after oral administration within the recommended clinical dosage range (Pfizer Inc. 2020). The elimination half-life of intramuscular ziprasidone is less than 3 hours with a single dose (Brook *et al.* 2000). Ziprasidone is cleared primarily via three metabolic pathways to yield four major circulating metabolites. Elimination occurs primarily through hepatic metabolism, with less than one-third of metabolic clearance mediated via cytochrome P450 (CYP)-catalyzed oxidation and approximately two-thirds via reduction of the parent compound by aldehyde oxidase to dihydroziprasidone, which then undergoes *S*-methylation. The literature reports no commonly encountered clinically significant pharmacological inhibitors of aldehyde oxidase, which suggests limited real-world potential for drug-drug interactions that would alter the clinical activity of ziprasidone (Obach *et al.* 2004).

Additional secondary metabolic pathways include *N*-dealkylation (via CYP3A4 and CYP1A2) and direct *S*-oxidation (via CYP3A4) (Beedham *et al.* 2003; Prakash *et al.* 2000). *S*-methyl-dihydroziprasidone is the only active metabolite, with lower D_2 receptor affinity and no significant binding to H_1, M_1, or a_1- and a_2-adrenergic receptors. A small amount of the parent compound is excreted unchanged in the urine (< 1%) and feces (< 4%).

There are no clinically significant age-or sex-related differences in the pharmacokinetics of oral ziprasidone (Pfizer Inc. 2020). Hepatic impairment might be expected to increase the AUC. A multiple-dose study (Everson *et al.* 2000) comparing subjects with clinically significant (Child-Pugh class A and B) cirrhosis and healthy control subjects indicated that 12 hours after administration of ziprasidone, the AUC was 13% and 34% greater in subjects with Child-Pugh class A and B cirrhosis, respectively, than in matched control subjects, which suggests that dosage adjustments are generally not mandatory for patients with hepatic impairment. Impairment in renal function is unlikely to significantly alter the pharmacokinetics of oral ziprasidone, which suggests that ziprasidone would not be removed by hemodialysis (Pfizer Inc. 2020). Intramuscular ziprasidone has not been systematically evaluated in the elderly or in patients with hepatic or renal impairment. Intramuscular ziprasidone contains a cyclodextrin excipient that is cleared by renal filtration; thus, it should be administered with caution to patients with impaired renal function (Pfizer Inc. 2020).

A study of in vitro enzyme inhibition (Pfizer Inc. 2020) indicated that ziprasidone has very little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and is thus unlikely to interfere with the metabolism of other medications that rely on these enzymes for clearance. In vivo studies have indicated that ziprasidone has no effect on the pharmacokinetics of lithium, estrogen, progesterone, or dextromethorphan (Pfizer Inc. 2020). Less than one-third of ziprasidone clearance is mediated by CYP-catalyzed oxidation, and because of this one would not anticipate a substantial change in ziprasidone AUC during coadministration with CYP3A4 inhibitors or inducers. Aldehyde oxidase-mediated reduction constitutes the primary metabolic pathway for ziprasidone. As also noted previously, currently no clinically significant pharmacological inhibitors of aldehyde oxidase are commonly encountered (Obach *et al.* 2004). Consistent with this prediction, coadministration of ziprasidone with ketoconazole, a potent CYP3A4 inhibitor, results in only modest increases in ziprasidone AUC (33%) and C_{max} (34%) (Miceli *et al.* 2000b), whereas coadministration with carbamazepine, an inducer of CYP3A4, results in modest reductions in ziprasidone AUC (44%) and C_{max} (39%) (Miceli *et al.* 2000a). Coadministration with CYP2D6 inhibitors has no effect on ziprasidone plasma levels. Coadministration of ziprasidone with lithium results in no significant change in steady-state lithium levels (Apseloff *et al.* 2000), and commonly used antacids and cimetidine do not significantly alter ziprasidone pharmacokinetics (Pfizer Inc. 2020).

Indications and Efficacy

Schizophrenia and Schizoaffective Disorder

Ziprasidone is approved in the United States for short-term and maintenance treatment of schizophrenia. Its efficacy in the treatment of hospitalized patients with acute schizophrenia or schizoaffective disorder was demonstrated in a series of double-blind, placebo-controlled

trials of 4-6 weeks' duration (Daniel *et al.* 1999; Kane 2003b; Keck *et al.* 1998, 2001). Additional short-term (4-to 8-week) randomized, double-blind treatment studies using active antipsychotic comparator agents indicated that ziprasidone has efficacy comparable to that of haloperidol, risperidone, and olanzapine for the treatment of positive symptoms and overall psychopathology (Addington *et al.* 2004; Goff *et al.* 1998; Simpson *et al.* 2004a). In a pooled analysis of four short-term placebo-controlled trials and three active comparator trials, Murray *et al.* (2004) demonstrated that ziprasidone dosages of at least 120 mg/day, in comparison with lower dosages, are associated with a more rapid and favorable response in overall psychopathology as well as a lower discontinuation rate due to inadequate clinical response, which suggests the importance of rapid titration to at least 120 mg/day (Kane 2003b; McCue *et al.* 2006).

Suboptimal dosing, inadequate titration regimens, and failure to administer ziprasidone with food may have negatively affected its performance in some clinical trials. Some clinical trials included efficacy analyses of dosages that would now be considered suboptimal (i.e., < 120 mg/day), whereas other studies used prolonged titration of ziprasidone, with a therapeutic dosage not reached until 1 week or more into the study. Clinical trials conducted before the release of pharmacokinetic data by Lombardo *et al.* (2007) may not have been designed to ensure that ziprasidone was administered with food for optimal oral absorption.

Ziprasidone has also been studied for the treatment of early psychosis and schizophrenia. In a study by Johnsen *et al.* (2010), patients admitted to an emergency ward with early psychosis were consecutively randomly assigned to receive one of several different SGAs: ziprasidone, olanzapine, quetiapine, or risperidone. No clinically significant differences in the effectiveness of the tested antipsychotics emerged after a 2-year follow-up period. Crespo-Facorro *et al.* (2013, 2014), in a 12-week prospective, open-label, randomized trial followed by a year-long extension period comparing quetiapine, aripiprazole, and ziprasidone for the treatment of first-episode psychosis, found significantly greater discontinuation rates with quetiapine than with aripiprazole or ziprasidone, owing to insufficient efficacy of quetiapine and comparable efficacy of the other two tested agents.

The maintenance efficacy of ziprasidone in treating schizophrenia and schizoaffective disorder was studied in a series of double-blind and open-label extension trials (Arato *et al.* 2002; Hirsch *et al.* 2002; Kane 2003a; Schooler 2003; Simpson *et al.* 2002, 2004b). These studies indicated that long-term therapy with ziprasidone maintains clinical response and is effective in preventing relapse.

In two maintenance-of-effect studies, patients with schizophrenia or schizoaffective disorder who had previously demonstrated acute response to treatment (defined as a [?] 20% decrease in Positive and Negative Syndrome Scale [PANSS] total score and a Clinical Global Impression [CGI] Scale score of [?] 2) were randomly assigned to receive either ziprasidone or a comparator antipsychotic agent for at least 26 weeks (Addington *et al.* 2009; Schooler 2003; Simpson *et al.* 2002, 2005). In both of these studies, the ziprasidone treatment groups demonstrated significant improvements from baseline in overall psychopathology, as measured by mean changes in symptom ratings using PANSS total, PANSS-Negative subscale, Brief Psychiatric Rating Scale--Depression Factor (BPRS-D), and CGI-Severity (CGI-S) scores. These improvements were comparable to those seen in the olanzapine (Simpson *et al.* 2005) and risperidone (Addington *et al.* 2009) treatment groups.

To evaluate relapse prevention, the Ziprasidone Extended Use in Schizophrenia (ZEUS) study enrolled stable inpatients with chronic schizophrenia and randomly assigned participants to 1 year of treatment with ziprasidone 40 mg/day (n = 72), 80 mg/day (n = 68), or 160 mg/day (n = 67) or placebo (n = 71), with a planned primary Kaplan-Meier analysis of time to relapse (Arato *et al.* 2002). In this study, all three dosages of ziprasidone were superior to placebo in the prevention of relapse.

A number of long-term double-blind trials designed to examine the efficacy of ziprasidone in symptomatic patients with schizophrenia have been performed (Breier *et al.* 2005; Hirsch *et al.* 2002; Kinon *et al.* 2006; Simpson *et al.* 2004a, 2005). Hirsch *et al.* (2002) compared the efficacy of ziprasidone (n = 148) and haloperidol (n = 153) in a 28-week double-blind trial of stable outpatients with schizophrenia with prominent negative symptoms. In this study, ziprasidone and haloperidol were similarly efficacious in reducing overall psychopathology, with an advantage for ziprasidone in the percentage of patients classified as negative symptom responders. Breier *et al.* (2005) conducted a 28-week study of ziprasidone and olanzapine in outpatients as well as inpatients (N = 548) with active symptoms. In this study, olanzapine treatment was associated with greater improvement from baseline in total psychopathology scores (PANSS total score, the primary efficacy measure) compared with ziprasidone and a higher rate of criterion-level response to treatment. Simpson *et al.* (2004a) conducted a 6-week double-blind, parallel-design, flexible-dose comparison (N = 269) of ziprasidone (n = 136) and olanzapine (n = 133) in which patients who showed at least minimal response (CGI-Improvement [CGI-I] score [?] 2 or [?] 20% reduction in the PANSS total score) were enrolled in a 6-month double-blind continuation trial (Simpson *et al.* 2005). In both 6-week and 6-month analyses, no differences between the treatment groups were detected on any primary (e.g., BPRS total score, CGI-S) or secondary (e.g., PANSS total score, CGI-I) measures.

Potkin *et al.* (2009) compared the effects of ziprasidone and haloperidol in a 196-week double-blind study using the Andreasen criteria for remission (Andreasen *et al.* 2005) by longitudinal analysis. During the initial 40-week study, no differences in PANSS or Global Assessment of Functioning (GAF) Scale score changes between the two antipsychotics compared emerged. In a subsequent 3-year extension study, ziprasidone-treated subjects were more likely to achieve remission (51%) compared with haloperidol-treated subjects (40%). The PANSS total and GAF score trajectories favored the higher 80-160 mg/day ziprasidone dosage as opposed to lower dosages, and the superior outcome for ziprasidone versus haloperidol may have been due in part to tolerability and adherence advantages.

There have been a number of effectiveness studies involving ziprasidone and using various definitions of *effectiveness*. Two are noted here. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies, funded by the National Institute of Mental Health, included a long-term, double-blind, randomized study of patients with schizophrenia (*N* = 1,493; Lieberman *et al.* 2005). Phase 1 of the CATIE schizophrenia study compared ziprasidone, olanzapine, quetiapine, risperidone, and perphenazine on a primary endpoint of time to discontinuation for lack of efficacy or for any cause. Because of the timing of its FDA approval, ziprasidone was added to the study after enrollment had begun for all other treatment arms; this resulted in a smaller sample size for the ziprasidone treatment arm and some limitations regarding conclusions about ziprasidone in phase 1 of the study.

The primary analysis for the phase 1 study detected significant differences in time to discontinuation across the treatment groups overall. The longest time to discontinuation was in the olanzapine group. In the total study sample, no significant differences were seen in the time to discontinuation between the ziprasidone and olanzapine treatment groups or between the ziprasidone group and the other antipsychotic treatment groups. However, fewer patients who entered the CATIE schizophrenia study were currently (i.e., prior to study entry) taking the relatively newly available ziprasidone compared with the number of patients taking the other antipsychotic medications in the trial. Supplemental analysis of phase 1 CATIE data by Essock *et al.* (2006) indicated the overall importance, in terms of subsequent discontinuation rates, of whether randomized subjects were switching medications or whether the study randomization allowed them to continue receiving their prior treatment. A significantly higher rate of subsequent discontinuation was observed in patients who actually made a medication switch compared with those who were randomly assigned to stay with the same medication they had been taking prior to the trial. This effect of switching medications therefore favored treatment arms with a larger percentage of nonswitchers (i.e., olanzapine and risperidone recipients in the CATIE phase 1 study). In a reanalysis of phase 1 CATIE data that excluded those patients randomly assigned to continue taking the antipsychotic they were already taking at baseline, Essock *et al.* (2006) found that differences between rates of discontinuation in the ziprasidone group and in the other antipsychotic groups were attenuated, and no statistically significant differences in the primary outcome measure were observed for any agent.

The Ziprasidone Experience in Schizophrenia in Germany/Austria (ZEISIG) study investigated the effectiveness of ziprasidone as measured by discontinuation rates and mean change in the BPRS total score in moderately ill and reasonably stable patients (*N* = 276) with schizophrenia or schizoaffective disorder (Kudla *et al.* 2007). Approximately 60% of subjects discontinued ziprasidone prematurely, most within the first 4 weeks of study treatment. In this study, ziprasidone use was initiated at a dosage of 40 mg/day. The relatively high rate of discontinuation may be explained in part by the planned dosing strategy.

Bipolar Disorder

Ziprasidone has received regulatory approval (e.g., from the FDA) as a monotherapy for the acute treatment of manic or mixed episodes in bipolar

I disorder, with acute efficacy demonstrated in two double-blind, placebo-controlled trials, each 3 weeks in duration, in patients with bipolar I disorder (Keck *et al.* 2003b; Potkin *et al.* 2005). In both studies, the onset of action was rapid (within 48 hours) and sustained through 3 weeks of treatment in patients with bipolar mania or bipolar mixed states, with or without psychotic symptoms. At endpoint, approximately half of the treated patients from both studies had symptom improvement that met response criteria for mania ([?] 50% reduction in Mania Rating Scale [MRS] scores).

A number of placebo-controlled trials evaluating the efficacy of short-term monotherapy with various antipsychotics, including haloperidol, ziprasidone, olanzapine, risperidone, quetiapine, and aripiprazole, have demonstrated comparable improvement in symptoms of mania (Bowden *et al.* 2005; Hirschfeld *et al.* 2004; Keck *et al.* 2003a, 2003b; Khanna *et al.* 2005; McIntyre *et al.* 2005; McQuade *et al.* 2003; Potkin *et al.* 2005; Sachs *et al.* 2006; Smulevich *et al.* 2005; Tohen *et al.* 1999, 2000; Vieta *et al.* 2010; Weisler *et al.* 2003). Regulatory approvals for individual agents have supported the efficacy and safety of a number of individual antipsychotics for acute treatment.

Mixed episodes (dysphoric mania) represent a common and often difficult-to-treat subset of bipolar mania that can be associated with significant depressive symptoms. Pooled data from a post hoc analysis of two similarly designed 3-week placebo-controlled trials (Stahl *et al.* 2010) in patients with acute bipolar mania indicated that ziprasidone significantly improved both depressive symptoms and symptoms of manic mood in patients with dysphoric mania. A meta-analysis by Muralidharan *et al.* (2013) supported the conclusion that some SGAs, including ziprasidone, are effective for the treatment of mixed states of bipolar disorder with predominant manic symptoms.

Two 52-week open-label extension studies supported the safety, tolerability, and sustained efficacy of ziprasidone as maintenance treatment for bipolar I disorder as adjunctive therapy to lithium or valproate (Keck *et al.* 2004, 2009; Weisler *et al.* 2004). The FDA has approved this indication. Keck *et al.* (2004) reported that treatment with ziprasidone (*n* = 127; mean dosage 123 mg/day) was associated with significantly lower MRS and CGI-S scores compared with baseline, beginning as early as the first week. Overall, improvements in manic symptoms achieved during acute treatment continued to consolidate during maintenance treatment with ziprasidone. During 52 weeks of treatment, only 6% of patients discontinued ziprasidone use because of a relapse of mania. Similarly, only 4% of patients discontinued because of a clinical switch into depression. An important caveat regarding these results is that a high rate of attrition was observed by the end of 1 year, which is consistent with long-term studies involving other SGAs but still limits full interpretation of the results. Comparable results were observed in a separate extension study of adjunctive ziprasidone therapy (mean dosage 92.6 mg/day) by Weisler *et al.* (2004); this study reported a mean improvement from baseline in MRS scores at all points throughout the study (Patel and Keck 2006). Finally, subjects with DSM-IV (American Psychiatric Association 1994) bipolar I disorder who achieved 8 or more consecutive weeks of stability with open-label ziprasidone (80-160 mg/day) adjunctive to lithium or valproate were randomly assigned in a 6-month double-blind maintenance period to receive ziprasidone plus mood stabilizer or placebo plus mood stabilizer. The time to intervention for a mood episode and the time to discontinuation for any reason were significantly longer for ziprasidone compared with placebo (Bowden *et al.* 2010), which indicates that ziprasidone is useful in combination with a classic mood stabilizer for maintenance of euthymia in bipolar disorder.

Treatment-Resistant Depression

A randomized, double-blind, placebo-controlled study, as well as a series of uncontrolled studies, has stimulated interest in the efficacy of ziprasidone for treating depression, especially treatment-resistant depression (Barbee *et al.* 2004; Jarema 2007; Papakostas *et al.* 2004, 2015). Papakostas *et al.* (2004) reported the results of a small study of 20 patients with major depressive disorder resistant to treatment with selective serotonin reuptake inhibitors. Open-label treatment with ziprasidone for 6 weeks, adjunctive to ongoing treatment with selective serotonin reuptake inhibitors, was evaluated with an intent-to-treat analysis that identified 10 treatment responders (defined as subjects with a [?] 50% decrease in depressive symptoms as measured by the 17-item version of the Hamilton Rating Scale for Depression [Ham-D-17]). In order to further evaluate these effects, a randomized, double-blind, placebo-controlled trial was conducted to compare adjunctive ziprasidone with adjunctive placebo among 139 adult outpatients with major depressive disorder who had not responded to an 8-week open-label trial of escitalopram alone (Papakostas *et al.* 2015). Compared with the patients who were randomly assigned to receive adjunctive placebo, those assigned to receive adjunctive ziprasidone (mean dosage 98 mg/day; SD = 40) with escitalopram demonstrated significantly greater rates of clinical response as well as significantly greater improvement in the Ham-D-17 total score and the Hamilton Anxiety Scale score. Ziprasidone has also been tested in non-treatment-resistant depression. A 12-week randomized, double-blind, placebo-controlled sequential parallel comparison trial of ziprasidone as monotherapy for major depressive disorder in 120 outpatients with depression conducted by Papakostas *et al.* (2012) showed no significant efficacy for ziprasidone compared with placebo. The authors suggested that a larger trial may be required to detect significant differences.

Agitation

The efficacy of intramuscular ziprasidone for the treatment of acutely agitated patients with schizophrenia was demonstrated in two randomized double-blind trials (2 mg IM vs. 10 mg or 20 mg IM, respectively, with up to three more doses allowed as needed at 4-hour or 2-hour intervals, respectively), which led to regulatory approval by the FDA (Daniel *et al.* 2001; Lesem *et al.* 2001). Treatment with single 10-or 20-mg doses leads to rapid reductions in symptom severity, with most patients having remission of agitation within 1 hour of dosing. Treatment with intramuscular ziprasidone is associated with a relatively low rate of concomitant benzodiazepine use (< 20%) and may be better tolerated than treatment with haloperidol (Zhang *et al.* 2013). Sequential use of intramuscular ziprasidone followed by oral ziprasidone for the treatment of acute psychotic agitation demonstrated superior efficacy, compared with sequential use of intramuscular and oral haloperidol, in two 7-day randomized open-label trials (Brook *et al.* 2000; Swift *et al.* 1998) as well as in a 6-week randomized, single-blind, flexible-dose study (Brook *et al.* 2005). Clinical improvement occurred more rapidly with ziprasidone than with haloperidol in one study and as quickly as 30 minutes after the first intramuscular administration of ziprasidone (Swift *et al.* 1998). Cumulative data from these studies indicate that intramuscular ziprasidone can rapidly control agitation and psychotic symptoms and can provide greater mean improvements in acute agitation than those seen with intramuscular haloperidol (e.g., greater mean improvements in the BPRS total score, agitation, and the CGI-S score [Brook 2003]).

Use in Pediatric Populations

Ziprasidone is not approved by the FDA for use in pediatric patients in the United States. Its use has been evaluated in children and adolescents (ages 10-17 years) experiencing manic or mixed episodes associated with bipolar disorder (Kuehn 2009). In the European Union (European Medicines Agency), ziprasidone has been approved for the treatment of bipolar disorder (mania) in pediatric patients ages 10-17 years. Results have been reported from randomized controlled trials (RCTs) of ziprasidone in children and adolescents (ages 10-17 years) with bipolar disorder

(Versavel *et al.* 2005) and with bipolar disorder, schizophrenia, or schizoaffective disorder (DelBello *et al.* 2008). In one study, treatment with ziprasidone was associated with improvement in mania and overall psychopathology (Versavel *et al.* 2005). Another study focused on safety and did not report any unexpected tolerability findings in this age group for a starting dosage of 20 mg/day titrated to between 80 mg/day and 160 mg/day over 1-2 weeks for clinically determined optimal dosing (DelBello *et al.* 2008). Finally, a 4-week acute randomized, placebo-controlled multicenter trial, followed by a 26-week open-label extension study, in pediatric patients with bipolar disorder (ages 10-17 years) showed benefits of ziprasidone and a benign short-term side-effect profile (Findling *et al.* 2013a). In a study of pediatric schizophrenia using a 6-week randomized (2:1), double-blind, placebo-controlled design, ziprasidone did not separate from placebo (Findling *et al.* 2013b).

Side Effects and Toxicology

Ziprasidone has a favorable tolerability profile according to both short-and long-term clinical trials (Daniel 2003). The four most common treatment-related adverse events associated with oral ziprasidone in short-term premarketing placebo-controlled trials for schizophrenia were somnolence (14%), EPS (14%), nausea (10%), and constipation (9%) (Pfizer Inc. 2020). In subsequent clinical trials, treatment with ziprasidone was associated with a low occurrence of adverse events, most of which were considered mild to moderate in severity (Arango *et al.* 2007; Arato *et al.* 2002; Lieberman 2007; Nemeroff *et al.* 2005; Weiden *et al.* 2002, 2003b). In addition to the full U.S. prescribing information, which contains a comprehensive list of potential adverse events (Pfizer Inc. 2020), published case reports offer accounts of various rare adverse events that may be associated with the use of ziprasidone (Akkaya *et al.* 2006; Kaufman *et al.* 2006; Miodownik *et al.* 2005; Murty *et al.* 2002; Villanueva *et al.* 2006).

Intramuscular ziprasidone shows a favorable tolerability profile similar to that of oral ziprasidone. In premarketing trials of intramuscular ziprasidone, the most common side effects (those with an incidence of > 5% and an incidence greater than that seen in placebo recipients) were somnolence (20%), headache (13%), and nausea (12%) (Pfizer Inc. 2020). Pooled data from clinical trials of intramuscular ziprasidone indicated that most treatment-related adverse events were mild to moderate in severity, with the most common side effects being headache, nausea, dizziness, insomnia, anxiety, and pain at the injection site (Daniel 2003; Zimbroff *et al.* 2002).

Ziprasidone was previously considered a Category C drug in pregnancy. In December 2014, the FDA published a final rule on labeling for pregnancy and lactation that removed the letter category labeling and required drug labels to be updated when new information becomes available (U.S. Food and Drug Administration 2021). Although some specific developmental effects have been noted in animal studies at dosages ranging from 0.5 to 8.0 times the maximal recommended human dosage (Pfizer Inc. 2020), there is as yet no similar emerging evidence of such effects in humans. The reader is advised to consult the current U.S. prescribing information for a detailed list of potential adverse drug effects identified in the regulatory approval process and postmarketing surveillance.

In 2005, the FDA mandated the addition of a black box warning in the U.S. prescribing information regarding an increased risk of mortality associated with the use of both SGAs and first-generation antipsychotics (FGAs) in elderly patients with dementia-related psychosis. Observed causes of death have been varied, and the mechanism of any drug effect in schizophrenia remains uncertain. In particular, it remains unclear to what extent these uncontrolled observations of increased mortality are due to specific drug effects or to the advanced medical risk characteristics of patients with dementia or delirium who tend to receive these medications (Farber *et al.* 2000; Rochon *et al.* 2008). A retrospective cohort study among older adults exposed to antipsychotics did not find increased mortality associated with ziprasidone, in contrast with haloperidol, olanzapine, and risperidone (Gerhard *et al.* 2014). Retrospective analysis of intramuscular use of ziprasidone, olanzapine, or haloperidol in large matched cohorts of hospitalized patients, for example, did not indicate significant differences in mortality rates among the three cohorts (Holdridge *et al.* 2010).

In 2014, the FDA issued a warning that ziprasidone is one of more than 50 medications associated with a rare condition called drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. This potentially life-threatening hypersensitivity reaction presents as a skin rash with fever, eosinophilia, lymphadenopathy, and multiorgan inflammation. Patients who develop this constellation of symptoms during treatment with ziprasidone should be evaluated for possible DRESS syndrome, and if that syndrome is suspected, their medication should be discontinued (Cacoub *et al.* 2011).

Treatment with ziprasidone is associated with a relatively low risk of clinically significant increases in body weight. An analysis of available studies with this agent and other antipsychotics, both FGAs and SGAs (Allison *et al.* 1999), estimated a mean 0.04-kg weight gain over a 10-week treatment period with ziprasidone and identified ziprasidone as having one of the lowest estimated effects on body weight of the agents analyzed. In a 6-week RCT in patients with acute exacerbations of schizophrenia or schizoaffective disorder, treatment with ziprasidone 80 mg/day produced a median increase in body weight of 1 kg, compared with no change in median weight with ziprasidone 160 mg/day or placebo (Daniel *et al.* 1999). In a 28-week study of outpatients with schizophrenia, mean changes in body weight from baseline to endpoint were similar during treatment with ziprasidone (+ 0.31 kg) and haloperidol (+ 0.22 kg) (Hirsch *et al.* 2002). In a 28-week study comparing the effects of ziprasidone and olanzapine, ziprasidone-treated patients experienced a small decrease in mean body weight ([?] 1.12 kg) from baseline, compared with a statistically and clinically different 3.06-kg mean increase in body weight observed with olanzapine treatment (Hardy *et al.* 2003; Kinon *et al.* 2006). Reductions in body weight were also associated with ziprasidone treatment in the 1-year ZEUS study of patients with chronic, stable schizophrenia (Arato *et al.* 2002); this study reported mean decreases from baseline of 2.7 kg, 3.2 kg, and 2.9 kg with 40 mg/day, 80 mg/day, and 160 mg/day dosages of ziprasidone, respectively, compared with a 3.6-kg decrease observed with placebo treatment. Results from the phase 1 and phase 2 CATIE studies provided further confirmation that treatment with ziprasidone has a low intrinsic risk for producing clinically significant weight gain, with 6%-7% of ziprasidone recipients demonstrating a 7% or greater increase from baseline in body weight compared with, for example, 27%-30% of olanzapine recipients (Lieberman 2007; Stroup *et al.* 2006). In the phase 1 CATIE study, ziprasidone treatment was associated with a mean reduction in body weight of 0.14 kg (0.3 lb) per month of treatment, compared with mean increases of 0.91 kg, 0.23 kg, and 0.18 kg per month (2.0 lb, 0.5 lb, and 0.4 lb per month, respectively) during treatment with olanzapine, quetiapine, and risperidone, respectively, the other SGAs tested (Lieberman *et al.* 2005). A meta-analysis of pooled data from nine placebo-controlled RCTs suggested no significant differences in weight gain between patients treated with ziprasidone and those receiving placebo (Gao *et al.* 2013).

Both short-and long-term studies have shown that ziprasidone has minimal adverse effects on glucose levels, plasma insulin levels, insulin resistance, and fasting and nonfasting lipid levels (Daniel *et al.* 1999; Glick *et al.* 2001; Rettenbacher *et al.* 2006; Simpson *et al.* 2004a, 2005), in contrast to the adverse effects detected with some active comparators. For example, olanzapine treatment can produce statistically significant increases in fasting glucose and insulin levels (Glick *et al.* 2001; Hardy *et al.* 2003; Simpson *et al.* 2002, 2005). In the CATIE phase 1 study, ziprasidone treatment was associated with minimal drug exposure-adjusted mean increases in blood glucose (+ 2.9 +- 3.4 mg/dL) and hemoglobin A1c (+ 0.11 +- 0.09%) and decreases in plasma triglycerides ([?] 16.5+- 12.2 mg/dL) and total cholesterol ([?] 8.2 +- 3.2 mg/dL) (Lieberman 2007). In the CATIE phase 2 study, ziprasidone-treated patients showed minimal drug exposure-adjusted mean increases in blood glucose (+ 0.8 +- 5.6 mg/dL) and hemoglobin A1c (+ 0.46 +- 0.3%) and decreases in triglycerides ([?] 3.5 +- 20.9 mg/dL) and total cholesterol ([?] 10.7 +- 5.1 mg/dL) (Stroup *et al.* 2006).

A number of medications, including psychotropic medications, can increase the duration of the QTc interval (i.e., the QT interval corrected for heart rate). Basic research suggests plausible mechanisms by which an increase in the QTc interval could increase the risk of sudden cardiac death, and clinical investigations suggest that certain small subgroups of the general population may have an increased risk of sudden cardiac death--for example, individuals with a family history of congenital long QT syndrome (> 500 milliseconds) and those who concomitantly use drugs that markedly increase the QTc interval (e.g., by > 60 milliseconds) via either pharmacokinetic or pharmacodynamic interactions (Montanez *et al.* 2004). These potential risks have understandably led to regulatory interest in the effects of drugs on the QTc interval. It should be noted that epidemiological studies in the general population suggest that modest prolongations of the QTc interval are not a risk factor for cardiovascular mortality or sudden death, so any risk in the general population of modest QTc prolongations is likely to be small and difficult to detect reliably (Montanez *et al.* 2004). When considered alongside risks such as obesity, hypercholesterolemia, diabetes, hypertension, physical inactivity, or cigarette smoking, each with well-characterized effects in the general population, modest QTc prolongations do not represent a comparable risk factor for cardiovascular mortality or sudden death in the general population.

Against this background, thioridazine, following decades of use, was required to add to its prescribing information a black box warning related to its effects on prolonging the QTc interval. Other FGAs, including haloperidol, are also associated with some risk of QTc interval prolongation (Gury *et al.* 2000; O'Brien *et al.* 1999). The rate of occurrence of torsades de pointes with FGAs has been estimated as "10-15 such events in 10,000 person-years of observation" (Glassman and Bigger 2001, p. 1774). Ziprasidone, like certain other antipsychotic agents, can induce orthostatic hypotension, in particular early in treatment exposure, which can lead to transient tachycardia, dizziness, or syncope (Swainston Harrison and Scott 2006). However, tachycardia has been observed to be infrequent and to be as common as in patients treated with placebo (Swainston Harrison and Scott 2006). Tachycardia and syncope related to hypotension need to be distinguished from the ventricular arrhythmias that in rare cases can occur in relation to QTc interval prolongation.

Ziprasidone treatment has been demonstrated to result in a modestly increased risk of QTc interval prolongation (Pfizer Inc. 2020). This QTc interval prolongation at C_{max} (mean increase > 15 milliseconds) is 9-14 milliseconds greater than that seen with risperidone, olanzapine, quetiapine, or haloperidol but approximately 14 milliseconds less than that seen with thioridazine. Unlike with thioridazine, the modest effect of ziprasidone on the QTc interval is not worsened by the presence of commonly encountered inhibitors of drug metabolism. In clinical trials of ziprasidone monotherapy that reported QTc interval changes, in studies of high-dosage intramuscular administration, and in case reports of ziprasidone overdose, there was no evidence of any significant clinical sequelae such as torsades de pointes or sudden death (Arato *et al.* 2002; Arbuck 2005; Daniel 2003; Gomez-Criado *et al.* 2005; Harrigan *et al.* 2004; Insa Gomez and Gutierrez Casares 2005; Levy *et al.* 2004; Lieberman 2007; Miceli *et al.* 2004, 2010; Montanez *et al.* 2004; Nemeroff *et al.* 2005; Tan *et al.* 2009; Taylor 2003; Weiden *et al.* 2002, 2003a). These findings are consistent with analyses of large population samples, which have failed to demonstrate any association between QTc interval duration and either cardiovascular or all-cause mortality (Goldberg *et al.* 1991).

Rare cases of torsades de pointes have been reported with a number of different medications, including ziprasidone, but the incidence of these events appears to be below the known prevalence of torsades de pointes in community-based population samples (Heinrich *et al.* 2006). The U.S. prescribing information for ziprasidone suggests that clinicians should nonetheless be cognizant of this potential risk and be aware of circumstances that may increase the risk of torsades de pointes and/or sudden death in association with the use of any drugs that can prolong the QTc interval. Such circumstances include the presence of bradycardia, hypokalemia, or hypomagnesemia; concomitant use of other medications known to cause clinically significant QT prolongation (although an additive effect with ziprasidone has not been established); and the presence of congenital long QT syndrome. The U.S. prescribing information further states that ziprasidone should not be used by patients who have significant cardiovascular conditions, such as uncompensated heart failure or a cardiac arrhythmia, or by those who have had a recent acute myocardial infarction or persistent QTc interval measurements of greater than 500 milliseconds, and the prudent clinician might consider using the same caution when prescribing many other antipsychotic and psychotropic medications currently in use. A comprehensive review of the cardiac safety of antipsychotics (Hasnain and Vieweg 2014) reached a similar conclusion--that little evidence exists that antipsychotic drug-associated QTc interval prolongation is in itself sufficient to cause torsades de pointes in the absence of other risk factors that facilitate or attenuate the progression of drug-associated QTc interval prolongation to torsades de pointes.

Summary for Ziprasidone

Ziprasidone was the fourth atypical antipsychotic following clozapine to become available in the United States. This agent has a unique pharmacological profile, with the highest 5-HT_{2A}/D_2 affinity ratio among currently available agents, potent serotonin and norepinephrine reuptake inhibition activity, agonist activity at 5-HT_{1A} receptors, and clinically relevant antagonist activity at various 5-HT_2 receptor subtypes. Ziprasidone has demonstrated rapid onset and sustained efficacy for the treatment of schizophrenia, schizoaffective disorder, and bipolar mania, with promising evidence of favorable mood, cognitive, and prosocial effects. It is available in an intramuscular formulation for the treatment of acute agitated psychosis and was approved by the European Medicines Agency, but not the FDA, for use in treating bipolar mania in children and adolescents 10-17 years of age.

Ziprasidone has highly favorable safety and tolerability profiles with limited potential for drug-drug and drug-disease interactions--critical issues for a patient population that generally has a high burden of medical comorbidity and is commonly exposed to complex polypharmacy. The adverse-effect profile of ziprasidone is particularly noteworthy in areas that are key to safety and tolerability for patients with major mental disorders such as schizophrenia and bipolar disorder, in that it includes low drug-related risk for acute EPS and minimal effects on cardiometabolic risk factors such as obesity and dyslipidemia.

Asenapine

History and Discovery

Asenapine is available in two relatively novel formulations: as a sublingual tablet and as a transdermal patch. Sublingual asenapine was initially approved by the FDA in August 2009 for the treatment of acute schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults. It was subsequently approved for maintenance treatment of schizophrenia in adults, for adjunctive use with lithium or valproate in the treatment of acute manic or mixed episodes associated with bipolar I disorder in adults, and as a monotherapy for bipolar mania in pediatric patients (ages 10-17 years [Allergan USA 2021]). In addition to the original unflavored formulation, a black-cherry-flavored version of sublingual asenapine was approved for the U.S. market in 2010 and is currently available as 2.5-, 5-, and 10-mg tablets.

Asenapine transdermal system (Secuado; manufactured by Hisamitsu Pharmaceutical Co., Inc., and distributed by Noven Therapeutics) was approved by the FDA in October 2019 and is currently available in patch strengths of 3.8, 5.7, and 7.6 mg/24 hours (equivalent to asenapine sublingual tablets 5 mg bid, 7.5 mg bid, and 10 mg bid, respectively). It is the first patch to become available in the United States for the treatment of adults with schizophrenia (Musselman *et al.* 2021). This formulation potentially simplifies the use of this antipsychotic by reducing the dosing frequency from twice daily (recommended for the sublingual tablet) to once daily (recommended for the patch). With the patch there are no food and drink restrictions, and dysgeusia (distorted or bad taste) and hypoesthesia of the tongue are avoided.

Structure-Activity Relations and Pharmacological Profile

Asenapine is a second-generation (atypical) antipsychotic that belongs to the chemical class of dibenzo-oxepino pyrroles (Figure 31-2).

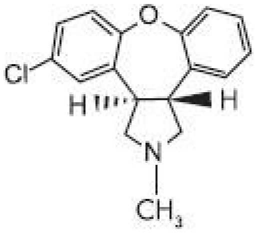

FIGURE 31-2. Chemical structure of asenapine.

Asenapine's receptor binding profile is notable for high affinity (K_i [values in nM]) for several serotonin receptor subtypes, including 5-HT_{2C} (0.03), 5-HT_{2A} (0.06), 5-HT_7

(0.13), 5-HT_{2B} (0.16), and 5-HT_6 (0.25), and for several dopamine receptor subtypes, including D_3 (0.42), D_2 (1.3), D_1 (1.4), and D_4 (1.1) (Allergan USA 2021; Shahid *et al.* 2009). Asenapine has high binding affinities to H_1 (1.0) receptors and to norepinephrine a_1 (1.2) and a_2 (1.2) receptors. It binds with somewhat lower affinity to 5-HT_5 (1.6), 5-HT_{1A} (2.5), and 5-HT_{1B} (4.0) receptors and H_2 (6.2) receptors. It binds very weakly to M_1 (8,128) receptors. Asenapine acts as an antagonist at all of these receptors.

Asenapine has approximately 38 metabolites, none highly prevalent. These metabolites have few clinically relevant effects either because of their lower affinity for the relevant receptors or because of their inability to cross the blood-brain barrier (Citrome 2009a, 2014a; U.S. Food and Drug Administration 2009). Although the precise mechanism of action of asenapine in the treatment of schizophrenia is unknown, it is thought that antagonism at the D_2 and 5-HT_{2A} receptors mediates the drug's antipsychotic activity (Allergan USA 2021). In studies using PET, asenapine demonstrated dose-dependent D_2 receptor occupancy (dose range 0.1-4.8 mg), with a significant correlation between D_2 occupancy and plasma concentration (U.S. Food and Drug Administration 2009). Sublingual administration of 4.8 mg bid results in a mean D_2 occupancy of 79% approximately 3-6 hours after dosing.

Pharmacokinetics and Drug-Drug Interactions

When administered orally, asenapine is absorbed primarily in the oral mucosa. It is formulated as a highly porous, rapidly dissolving tablet for sublingual administration, with a resulting bioavailability of approximately 35% (Schering-Plough Research Institute 2009; U.S. Food and Drug Administration 2009). If the tablet is swallowed rather than allowed to dissolve orally, the drug's bioavailability is reduced to less than 2% because of high hepato-gastrointestinal first-pass metabolism (Allergan USA 2021; U.S. Food and Drug Administration 2009). Patient instructions are to place the tablet under the tongue and to refrain from eating or drinking for 10 minutes after administration, because drinking water sooner than 10 minutes can result in reduced bioavailability of asenapine (Allergan USA 2021).

Although asenapine was developed for sublingual administration, absorption will occur even if the tablet is placed elsewhere in the oral cavity, as was demonstrated in a study of healthy men who received single 5-mg doses of asenapine via sublingual, supralingual, and buccal routes (Gerrits *et al.* 2010). Drug exposure with buccal administration (i.e., cheeking) as measured by plasma levels was almost 25% higher than that with sublingual administration, whereas exposure with supralingual administration was 6% lower. However, these differences in exposure by oral administration site are small in relation to the wide variability in asenapine's pharmacokinetics observed across the clinical studies used to obtain regulatory approval, in which overall exposure varied by 37%, with a mean interindividual variability of 26% and a mean intraindividual variability of 26% (U.S. Food and Drug Administration 2009). Doubling the sublingually administered dosage from 5 mg to 10 mg bid results in less than linear (1.7 times) increases in both the amount of exposure and the maximal concentration (Allergan USA 2021).

Peak plasma levels are reached 30-90 minutes after sublingual administration, and asenapine has a mean terminal half-life of approximately 24 hours (Allergan USA 2021; Schering-Plough Research Institute 2009; U.S. Food and Drug Administration 2009). Clinical trials supporting the approval of sublingual asenapine were conducted using twice-daily dosing, which resulted in the recommendation for twice-daily dosing in the product labeling. However, barring tolerability issues when starting treatment with asenapine, once-daily dosing in the evening may be feasible given the half-life.

The pharmacokinetic profile of the transdermal asenapine system demonstrates dose-proportional kinetics and sustained delivery of asenapine with a low peak-to-trough plasma level ratio (Suzuki *et al.* 2021). Asenapine transdermal system is available in three patch sizes--20 cm^2 (3.8 mg/24 hours), 30 cm^2 (5.7 mg/24 hours), and 40 cm^2 (7.6 mg/24 hours)--

that deliver the equivalent of sublingual asenapine 5 mg bid, 7.5 mg bid, and 10 mg bid (Noven Therapeutics 2022).

Asenapine is metabolized in the liver primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by CYP isoenzymes (predominantly CYP1A2). Asenapine has a large volume of distribution and is highly bound (95%) to plasma proteins, including albumin and a_1-acid glycoprotein. Despite the fact that smoking can induce CYP1A2, concomitant smoking had no substantial effect on the pharmacokinetics of asenapine when tested in healthy male subjects (U.S. Food and Drug Administration 2009). Fluvoxamine, a potent CYP1A2 inhibitor, can increase exposure to asenapine by 29% and therefore should be coadministered with caution (Allergan USA 2021).

Use of asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh class C). Asenapine exposure is on average seven times higher in patients with severe impairment than in those with normal hepatic function. However, no dosage adjustment is required in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. No dosage adjustment is required for patients with renal impairment.

Asenapine can inhibit CYP2D6, resulting, for example, in twofold increases in paroxetine concentrations (U.S. Food and Drug Administration 2009). The product label advises caution when coadministering asenapine with drugs that are both substrates and inhibitors of CYP2D6 (Allergan USA 2021).

Indications and Efficacy

Sublingual asenapine's efficacy in treating acute schizophrenia in adults was tested in four pivotal short-term randomized, double-blind, placebo-and active comparator-controlled multicenter studies (Citrome 2011b, 2014b). Two studies were accepted by the FDA as supportive of asenapine's efficacy in the acute treatment of schizophrenia in adults (Kane *et al.* 2010; Potkin *et al.* 2007). The efficacy of transdermal asenapine in treating acute schizophrenia was established in a 6-week Phase III randomized, placebo-controlled inpatient study in which asenapine transdermal system (3.8 mg/

24 hours and 7.6 mg/24 hours) demonstrated significant improvement versus placebo at week 6 for the primary endpoint (PANSS total score) and key secondary endpoints (Citrome *et al.* 2020). Transdermal asenapine has neither been tested in, nor approved for, any indication other than schizophrenia.

Sublingual asenapine's efficacy in the treatment of manic or mixed episodes of bipolar I disorder in adults was supported in both of two completed Phase III randomized, placebo-and active comparator-controlled 3-week trials (McIntyre *et al.* 2009a, 2010a). Approximately 1 year after the initial approval of asenapine for these indications, the FDA approved asenapine for the maintenance treatment of schizophrenia (on the basis of a double-blind, placebo-controlled multicenter clinical trial [Kane *et al.* 2011]) and for use as adjunctive therapy with either lithium or valproate in the acute treatment of manic or mixed episodes associated with bipolar I disorder (again on the basis of a placebo-controlled trial [Szegedi *et al.* 2012]). Approval of asenapine for the treatment of bipolar mania in pediatric patients (ages 10-17 years) was obtained in 2015 on the basis of a placebo-controlled trial (Findling *et al.* 2015b).

In adults, the recommended dosage of sublingual asenapine for acute schizophrenia is 5 mg bid; that for bipolar manic or mixed episodes is 10 mg bid (5 mg bid if the drug is administered with lithium or valproate) on the basis of the clinical trials used to obtain regulatory approval. Titration to these target dosages is not necessary. In a modeling and simulation study (Friberg *et al.* 2009), asenapine dosages of 5 and 10 mg bid had similar efficacy in the acute treatment of schizophrenia. In the maintenance study in schizophrenia on which asenapine's approval for that indication was based, the most commonly used dosage was 10 mg bid (Kane *et al.* 2011).

In pediatric patients (ages 10-17 years) with bipolar mania, the recommended starting dosage of sublingual asenapine as monotherapy is 2.5 mg bid, with increases up to 10 mg bid possible.

According to the product label for transdermal asenapine, the initial recommended dosage is 3.8 mg/24 hours (Noven Therapeutics 2022). The dosage may be increased to 5.7 mg/24 hours or 7.6 mg/24 hours, as needed, after 1 week.

Schizophrenia (Sublingual Asenapine)

In one of the two positive trials, 458 patients with acute schizophrenia were randomly assigned to fixed-dosage treatment with asenapine 5 mg bid, asenapine 10 mg bid, placebo, or an active control for assay sensitivity (haloperidol 4 mg bid) for 6 weeks (Kane *et al.* 2010). The primary efficacy endpoint was change from baseline in the PANSS total score (Kay *et al.* 1987). In analyses of the change in the PANSS total score, asenapine 5 mg bid and haloperidol were both superior to placebo, with statistically significant differences seen from day 21 onward. However, asenapine 10 mg bid did not demonstrate an advantage over placebo, a finding that the authors suggested may have been due in part to the high placebo response rate in this trial. Rates of response--defined as a minimum reduction of 30% in the PANSS total score or a CGI-I score of 1 (very much improved) or 2 (much improved)--were 55% for asenapine 5 mg bid, 49% for asenapine 10 mg bid, 43% for haloperidol, and 33% for placebo, yielding numbers needed to treat (NNTs; Citrome 2008) versus placebo of 5 for asenapine 5 mg bid, 7 for asenapine 10 mg bid, and 10 for haloperidol (Citrome 2011b).

In the other short-term acute schizophrenia trial that was considered positive and supportive of asenapine's efficacy, 182 patients were randomly assigned to asenapine 5 mg bid, placebo, or an active control for assay sensitivity (risperidone 3 mg bid) for 6 weeks (Potkin *et al.* 2007). The primary efficacy endpoint was change from baseline in the PANSS total score. Compared with placebo, asenapine produced significantly greater decreases in the PANSS total score from week 2 onward. Risperidone did not statistically significantly separate from placebo. Using the criterion of reduction in the PANSS total score of at least 30%, the researchers categorized 38% of the patients in the asenapine group as responders, compared with 39% of those in the risperidone group and 25% of those in the placebo group, yielding NNTs versus placebo of 8 for asenapine and 7 for risperidone (Citrome 2011b).

Two other 6-week acute schizophrenia trials were conducted (Citrome 2011b; U.S. Food and Drug Administration 2009). One trial was considered negative because asenapine 5 mg bid or 10 mg bid failed to separate from placebo, whereas the active control (olanzapine 15 mg/day) did separate from placebo. The other trial was considered a failed trial because neither asenapine 5 mg bid or 10 mg bid nor the active control (olanzapine 10-20 mg/day) separated from placebo. An additional double-blind trial was conducted in which 532 adult Asian participants from Japan, Korea, and Taiwan were randomly assigned to receive asenapine 5 mg bid, asenapine 10 mg bid, or placebo for 6 weeks (Kinoshita *et al.* 2016). The primary efficacy endpoint was change from baseline in the PANSS total score. Improvements from baseline in the PANSS total score were significantly greater among the patients receiving asenapine 5 mg bid or 10 mg bid, compared with those receiving placebo, from days 14 and 7, respectively. Using the criterion of reduction in the PANSS total score of at least 30%, the researchers categorized 39% of the patients in the asenapine 5-mg bid group and 44% of those in the 10-mg bid group as responders, compared with 21% of those in the placebo group, yielding NNTs versus placebo of 6 for asenapine 5-mg bid and 5 for asenapine 10-mg bid. An 8-week placebo-controlled, double-blind trial in 306 adolescent (ages 12-17 years) patients with schizophrenia failed to demonstrate asenapine's efficacy at dosages of 2.5 mg bid and 5 mg bid (Findling *et al.* 2015a).

Asenapine's longer-term efficacy in treating schizophrenia was examined in a published 1-year double-blind study in 1,225 individuals with schizophrenia or schizoaffective disorder. Patients were randomly assigned to receive asenapine (5 mg bid for the first week and then flexible dosing of 5 mg bid or 10 mg bid) or olanzapine (10 mg/day for the first week and then flexible dosing of 10 mg/day or 20 mg/day) (Schoemaker *et al.* 2010). The study had no placebo arm. Rates of discontinuation because of insufficient therapeutic effect were 25.1% for asenapine and 14.5% for olanzapine (NNT = 10 for olanzapine vs. asenapine to avoid discontinuation because of insufficient therapeutic effect). Changes from baseline in the PANSS total score were similar for asenapine and olanzapine at week 6 but showed a statistically significant difference in favor of olanzapine at endpoint (last observation carried forward analysis). Among the patients who completed the entire year-long trial (i.e., observed cases), changes in the PANSS total score were similar for asenapine and olanzapine at week 6 and at week 52. Completers were eligible to participate in an extension study in which clinical stability was further demonstrated (Schoemaker *et al.* 2012).

Asenapine's efficacy in the maintenance phase of schizophrenia was demonstrated in a published 26-week double-blind, placebo-controlled multicenter clinical trial (Kane *et al.* 2011). Patients were randomly assigned either to continue receiving asenapine or to receive placebo after establishing stability on asenapine during the 26 weeks of open-label treatment immediately prior. Of the 700 enrolled patients who were treated with open-label asenapine, 386 had symptoms that met stability criteria and entered the double-blind phase. Times to relapse/impending relapse and to discontinuation for any reason were significantly longer with asenapine than with placebo. The incidence of relapse or impending relapse was 12.1% for asenapine and 47.4% for placebo (NNT = 3). Completion rates were 69.6% for asenapine and 37.5% for placebo (NNT = 4). The most commonly used dosage of asenapine was 10 mg bid in both the open-label and the double-blind phase.

In two randomized, double-blind 26-week studies and their respective 26-week extensions, Buchanan *et al.* (2012) tested the hypothesis that asenapine is superior to olanzapine for treating persistent negative symptoms of schizophrenia and assessed the comparative long-term efficacy and safety of the two agents. Approximately 1,000 subjects participated. In the two core studies, 26-week completion rates were 64.7% and 49.6% with asenapine versus 80.4% and 63.8%, respectively, with olanzapine. In the two extension studies, completion rates were 84.3% and 66.3% with asenapine versus 89.0% and 80.9%, respectively, with olanzapine. Asenapine was not superior to olanzapine in producing change in the 16-item Negative Symptom Assessment total score in either core study, but it was superior to olanzapine at week 52 in one of the extension studies. Weight gain was consistently lower with asenapine. The incidence of EPS-related adverse events was higher with asenapine, but change in the

Extrapyramidal Symptom Rating Scale--Abbreviated total score did not differ significantly between treatments.

Schizophrenia (Transdermal Asenapine)

The efficacy of transdermal asenapine in treating acute schizophrenia was evidenced in a 6-week Phase III randomized, placebo-controlled study in which 614 inpatients were randomly assigned to receive transdermal asenapine 3.8 mg/24 hours (*n* = 204), transdermal asenapine 7.6 mg/24 hours (*n* = 204), or placebo (*n* = 206) (Citrome *et al.* 2020). Both asenapine dosages demonstrated statistically significant improvement versus placebo at week 6 for the primary endpoint (PANSS total score) and key secondary endpoints, with a greater magnitude of effect for the lower dosage. The lower dosage began to separate from placebo on the PANSS and CGI-S at week 2, and the higher dosage began to separate on the PANSS at week 3 and on the CGI-S at week 2. Rates of PANSS response (defined as a minimum reduction of 30% in the PANSS total score) were 30.8% for asenapine 3.8 mg/24 hours, 29.6% for asenapine 7.6 mg/24 hours, and 18.7% for placebo, yielding NNTs versus placebo of 9 and 10 for the lower dosage and higher dosage, respectively.

Rates of CGI-I response (defined as a score of 1 [very much improved] or 2 [much improved]) were 49.8% for asenapine 3.8 mg/24 hours, 43.3% for asenapine 7.6 mg/24 hours, and 34.0% for placebo, yielding NNTs versus placebo of 7 and 11 for the lower dosage and higher dosage, respectively.

A post hoc analysis on symptoms of hostility suggested that transdermal asenapine has a specific antihostility effect, a finding that was independent of sedation (Citrome *et al.* 2022).

Bipolar Disorder (Sublingual Asenapine)

In two identically designed 3-week acute studies of asenapine in the treatment of bipolar manic or mixed episodes (McIntyre *et al.* 2009a, 2010a), 977 subjects were randomly assigned to receive flexibly dosed asenapine 5-10 mg bid (starting dosage 10 mg bid), olanzapine 5-20 mg/day (starting dosage 15 mg/day), or placebo. The primary outcome measure for each of these studies was change from baseline in the Young Mania Rating Scale (YMRS; Young *et al.* 1978) total score. In the first study (McIntyre *et al.* 2009a), the YMRS total score was statistically significantly more improved from baseline to day 21 for asenapine and olanzapine compared with placebo. Sustained statistically significant improvement in the YMRS score compared with placebo was noted for asenapine and olanzapine from day 2 onward. Percentages of subjects whose symptoms met criteria for response (defined as a [?] 50% decrease from baseline in the YMRS total score) and remission (YMRS total score [?] 12) were higher with asenapine (42.3% and 40.2%, respectively) than with placebo (25.2% and 22.3%, respectively), yielding NNTs for response and for remission versus placebo of 6. The NNT for response for olanzapine versus placebo was 5, and that for remission was 6.

In the second study (McIntyre *et al.* 2010a), the YMRS total score also was statistically significantly improved from baseline to day 21 with asenapine and olanzapine compared with placebo, with sustained statistically significantly greater improvement in the YMRS total score versus placebo noted for asenapine and olanzapine from day 2 onward. In post hoc analyses, change in the YMRS total score from baseline to day 21 was significantly greater for olanzapine than for asenapine with last observation carried forward analysis but not with mixed models for repeated measures analysis. Rates of response (42.6%) and remission (35.5%) with asenapine did not differ significantly from those with placebo (34% and 30.9%, respectively), yielding NNTs of 12 and 22, respectively. Olanzapine was superior to placebo in rates of response (54.7%) and remission (46.3%), with NNTs for olanzapine versus placebo of 5 and 7, respectively, and NNTs for olanzapine versus asenapine of 9 and 10, respectively. On the basis of these studies, the recommended starting dosage of asenapine monotherapy for acute bipolar mania or mixed episodes in adults is 10 mg bid. However, additional information is available from a 3-week double-blind, placebo-controlled, fixed-dosage study of asenapine 5 mg bid and 10 mg bid in adults with an acute bipolar I disorder manic or mixed episode (Landbloom *et al.* 2016). Both asenapine dosages were statistically superior to placebo in mean change from baseline to day 21 in the YMRS total score, which suggests that 5 mg bid can be an adequate dosage for adults with acute bipolar mania or mixed episodes. However, in this trial, neither asenapine dosage had significantly more YMRS responders or remitters at day 21 than placebo.

Asenapine's longer-term efficacy in patients with manic or mixed episodes of bipolar disorder was assessed in a 9-week extension (McIntyre *et al.* 2009b) of the original two pivotal studies (McIntyre *et al.* 2009a, 2010a), followed by an additional 40-week extension (McIntyre *et al.* 2010b). A total of 504 participants received at least one dose of double-blind trial medication during the 9-week extension trial. These patients included 181 subjects who had been treated with asenapine and 229 who had been treated with olanzapine in the feeder trials (and who continued on the same treatment in the extension). In addition, 94 subjects who had been treated with placebo in the feeder trials were blindly allocated to receive asenapine 5-10 mg bid in the extension trial. The primary efficacy analysis demonstrated that asenapine was statistically not inferior to olanzapine as measured by change in the YMRS total score from baseline to day 84 for the observed case subjects who had 3 weeks of previous exposure to the study medication. The proportions of participants who were YMRS responders and remitters were similar in the asenapine and olanzapine groups: the rates of response at last observation carried forward endpoint were 77% and 82% with asenapine and olanzapine, respectively, and the rates of remission were 75% and 79%, respectively. Among 218 patients who were subsequently enrolled for another 40 weeks of double-blind treatment, maintenance of efficacy was observed with both asenapine and olanzapine, with no differences in response or remission rates between the two agents.

Another study tested the efficacy of asenapine 5 mg bid in the treatment of an acute manic or mixed episode when combined with lithium or divalproex over 12 weeks (Szegedi *et al.* 2012), and its findings supported this indication as approved by the FDA (Allergan USA 2021). Adjunctive asenapine produced significantly more improvement in mania than did placebo at week 3 (primary endpoint) and weeks 2-12. The YMRS response rates were similar at week 3 but significantly better with asenapine at week

12. The YMRS remission rates and changes from baseline on the CGI-Bipolar (CGI-BP) scale for mania and overall illness were significantly better with asenapine at weeks 3 and 12. Patients who completed the core study were eligible for a 40-week double-blind extension assessing safety and tolerability (Szegedi *et al.* 2012).

Asenapine's efficacy in the treatment of acute mania in pediatric patients (ages 10-17 years) was established in a single 3-week placebo-controlled, double-blind trial of 403 patients, of whom 302 received asenapine at fixed dosages of 2.5 mg bid, 5 mg bid, and 10 mg bid (Findling *et al.* 2015b). All patients were started on 2.5 mg bid, and dosages were titrated upward every 3 days in a stepwise fashion for patients randomly assigned to receive the higher dosages. Asenapine was statistically superior to placebo in improving the YMRS total and CGI-BP severity of illness scores. YMRS responder rates were 42%, 54%, and 52% for asenapine 2.5 mg bid, 5 mg bid, and 10 mg bid, respectively, versus 28% for placebo, yielding corresponding NNT values for asenapine versus placebo of 8, 4, and 5.

Agitation (Sublingual Asenapine)

Although asenapine is not specifically approved for this indication, it was tested for the management of agitation in an RCT (Pratts *et al.* 2014). Adults ages 18-65 years (*N* = 120, any diagnosis) manifesting agitation in an emergency department and found to have a score of [?] 14 on the PANSS-Excited Component (PANSS-EC) were randomly assigned to receive either a single sublingual 10-mg tablet of asenapine or matching placebo. Change in the PANSS-EC score at 2 hours was statistically significantly greater for the asenapine-treated subjects compared with the placebo-treated subjects, with an effect noted at 15 minutes, the earliest time point at which outcome was measured. The NNT value for response to asenapine versus placebo was 3, an effect size comparable to that observed in prior studies of intramuscular antipsychotics. This study awaits replication.

Side Effects and Toxicology

Common adverse reactions to sublingual asenapine observed in short-term trials (incidence [?] 5% and twofold greater than placebo) were akathisia, oral hypoesthesia (numbness), and somnolence in adult patients with schizophrenia; somnolence, dizziness, EPS other than akathisia, and increased weight for monotherapy in adult patients with bipolar manic or mixed episodes; and somnolence and oral hypoesthesia for adjunctive therapy in adult patients with bipolar manic or mixed episodes (Allergan USA 2021). Among the pediatric patients with bipolar disorder, common adverse reactions observed with sublingual asenapine as monotherapy were somnolence, dizziness, dysgeusia, oral paresthesias, nausea, increased appetite, fatigue, and increased weight (Allergan USA 2021).

Somnolence is the single most common adverse event associated with sublingual asenapine treatment, similar to all approved antipsychotic medications, although the magnitude of the effect varies by class. The product label describes this effect as usually transient, with the highest incidence reported during the first week of treatment (Allergan USA 2021). The highest rates of somnolence in adults were observed in the short-term acute manic/mixed-episode bipolar trials (most common dosage 10 mg bid), in which somnolence was reported in 24% of patients receiving asenapine versus 6% of patients receiving placebo, for a number needed to harm (NNH) of 6; rates of reported somnolence in the short-term schizophrenia trials (dosage 5 mg bid or 10 mg bid) were 13% for asenapine versus 7% for placebo, yielding an NNH of 17 (Citrome 2009a). Comparisons of other antipsychotics against placebo on the outcome of somnolence in short-term acute trials of schizophrenia yielded a broad range of incidence rates, resulting in NNH values that ranged from 7 for olanzapine or quetiapine extended release to a not statistically significant 42 for paliperidone (Citrome and Nasrallah 2012). Although somnolence was frequently reported, somnolence/sedation led to discontinuation in only a small proportion (0.6%) of adult patients treated with sublingual asenapine (Allergan USA 2021).

Dizziness can also occur and is attributable to asenapine's a_1-adrenergic antagonist activity; however, rates of syncope were observed to be low among patients, in contrast to rates observed among healthy volunteers in the clinical pharmacology trials (U.S. Food and Drug Administration 2009). Asenapine has a dose-related association with EPS and akathisia, although the frequency of these events is substantially lower with asenapine than with haloperidol (Citrome 2009a).

Unique to asenapine is the possibility of oral hypoesthesia, spontaneously reported as an adverse reaction in about 5% of the participants with acute schizophrenia in the clinical trials of the sublingual formulation (Allergan USA 2021). Directly asking patients about oral hypoesthesia may yield higher rates of this adverse effect, as was observed in a study that examined the effect of absorption site on the pharmacokinetics of asenapine in healthy male subjects (Gerrits *et al.* 2010). In this study, reported rates of oral paresthesias were 75.8%, 55.9%, and 45.7% for the sublingual, supralingual, and buccal absorption sites, respectively.

Asenapine has a mild effect on the QTc interval similar to that seen with quetiapine (Chapel *et al.* 2009, 2011). Hypersensitivity reactions have been reported with asenapine, in some cases occurring after the first dose, and this risk is now highlighted in the product labeling (Allergan USA 2021). Asenapine's effects on prolactin levels in the short-term schizophrenia and bipolar manic/mixed-episode studies in adults revealed no clinically relevant changes.

In the 6-week acute schizophrenia trials of sublingual asenapine, clinically relevant weight gain ([?] 7% over baseline body weight) was observed in 4.9% of subjects receiving asenapine versus 2% of those receiving placebo. In the 3-week acute bipolar manic/mixed-episode studies, clinically relevant weight gain was observed in 5.8% of subjects receiving asenapine versus 0.5% of those receiving placebo. In addition to a favorable weight gain profile, asenapine has shown minimal effects on glucose-related laboratory variables such as fasting glucose and fasting insulin (Schering-Plough Research Institute 2009).

Of interest are longer-term safety and tolerability comparisons of sublingual asenapine with other antipsychotics. In a 1-year double-blind RCT comparing asenapine with olanzapine (Schoemaker *et al.* 2010), the incidence of treatment-emergent adverse events was 82% in both groups. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine. The proportion of patients experiencing clinically relevant weight gain ([?] 7% over baseline) was approximately 35% for olanzapine and approximately 15% for asenapine (NNH = 5 for olanzapine vs. asenapine). No notable changes or between-group differences were seen in measures of total cholesterol or glucose, but triglyceride levels rose substantially with olanzapine and declined slightly with asenapine. In the 2-year blinded extension study (Schoemaker *et al.* 2012), mean body weight during the extension did not change beyond the weight gain in the core study. In the core study, EPS reported as adverse events were more common with asenapine (18%) than with olanzapine (8%) (NNH = 10 for asenapine vs. olanzapine). The most commonly reported type of movement disorder in the asenapine and olanzapine groups was akathisia, with treatment-emergent rates of 10% for asenapine and 4% for olanzapine (NNH = 17 for asenapine vs. olanzapine). In the 2-year blinded extension study, incidence rates of EPS-related adverse events that started during the extension were lower for both asenapine (4.5%) and olanzapine (3.3%) compared with those that started during the core study. Not many new cases of akathisia were reported during the extension period. There was little change in EPS severity during the extension of treatment.

Safety and tolerability outcomes are available from a 40-week extension of the acute bipolar trials (McIntyre *et al.* 2010b), in which clinically relevant weight gain occurred in 21.9%, 39.2%, and 55.1% of patients in the placebo/asenapine, asenapine, and olanzapine groups, respectively. The NNH for clinically relevant weight gain for olanzapine versus asenapine was 7. The percentage of patients shifting to above a prespecified akathisia global rating scale threshold was higher in the asenapine group compared with the placebo/asenapine and olanzapine groups.

Tolerability of asenapine in pediatric patients (ages 10-17 years) in the 3-week bipolar mania trial differed from that in the adult trials in terms of higher reported rates of somnolence, oral paresthesias (oral hypoesthesia, oral paresthesia, and oral dysesthesia), and weight gain (Allergan USA

2021). Rates of somnolence were 49% for asenapine (all dosages) versus 12% for placebo, yielding an NNH of 3, with no clear dose-response relationship. Rates of fatigue were substantially lower (9% and 5% for asenapine and placebo, respectively), but with a dose-response effect and a rate of 14% for subjects receiving asenapine 10 mg bid. Rates of oral paresthesias were 27% for asenapine (all dosages) versus 4% for placebo, yielding an NNH of 5. The proportions of patients experiencing clinically relevant weight gain ([?] 7% over baseline body weight) were 12%, 8.9%, and 8% for asenapine 2.5 mg bid, 5 mg bid, and 10 mg bid, respectively, versus 1.1% for placebo, yielding corresponding NNH values of 10, 13, and 15. A 50-week open-label, flexible-dose extension trial was available for those who completed the 3-week acute trial (Findling *et al.* 2016). Among the tolerability variables of interest, combined somnolence/sedation/hypersomnia occurred most frequently (42.4%). In total, 34.8% of the participants experienced clinically significant weight gain.

The systemic safety profile of transdermal asenapine in patients with schizophrenia was consistent with that of sublingual asenapine, absent the dysgeusia and hypoesthesia of the tongue observed with sublingual asenapine. The incidence of adverse reactions at the application site was higher for asenapine transdermal system (14.2%, 7.6 mg/24 hours; 15.2%, 3.8 mg/24 hours) than for placebo (4.4%). However, discontinuations due to application site reactions or skin disorders (urticaria, pruritus) were infrequent ([?] 0.5% per treatment group).

Summary for Asenapine

Asenapine's efficacy is evidenced both in short-term acute clinical trials and in longer-term studies. In the mind of the clinician, asenapine will likely be measured against other "metabolically friendly" SGAs such as ziprasidone, aripiprazole, iloperidone, lurasidone, brexpiprazole, and cariprazine, as well as newer agents in the antipsychotic development pipeline (Citrome 2011a, 2013, 2015). Differences among these choices include dosing factors (daily vs. twice-daily dosing, the need for dosage titration, special requirements for administration with or without food) as well as specific side-effect profiles.

The sublingual formulation of asenapine is unique in being the only antipsychotic that is absorbed primarily in the oral mucosa. Nonadherence by cheeking is minimized. The possibility of oral hypoesthesia and dysgeusia, a medication effect likely not experienced previously by the patient, necessitates advance warning. Asenapine transdermal system is the first patch available in the United States for the treatment of adults with schizophrenia. This formulation simplifies adherence by reducing the dosing frequency from twice daily (recommended for the sublingual tablet) to once daily (recommended for the patch) and avoids food and drink restrictions as well as dysgeusia and hypoesthesia of the tongue.

In summary, asenapine's place in the treatment of schizophrenia and bipolar manic or mixed episodes is likely to be in patients for whom metabolic concerns are of import and in patients who would prefer a sublingual or transdermal preparation. Substantial heterogeneity exists among the different antipsychotics and among individual patients (Volavka and Citrome 2009), so asenapine has a relevant place on a formulary. Cost may be an impediment to the use of asenapine, given the availability of inexpensive generic versions of risperidone, quetiapine, ziprasidone, and olanzapine in the United States as well as other generic SGAs in other countries.

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CHAPTER 32

Iloperidone

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History and Discovery

Approved by the FDA in 2009 for the treatment of schizophrenia, iloperidone meets the now generally appreciated profile of second-generation antipsychotics (SGAs) in that it has a complex pharmacology (with a predilection for dopamine and serotonin antagonism) and little propensity for extrapyramidal side effects (EPS), as well as efficacy against key symptoms of schizophrenia, as shown in placebo-controlled clinical trials (Rado and Janicak 2010; Weiden 2012). Iloperidone's efficacy has been demonstrated at a dosage range of 12-24 mg/day, with no clear advantage evident at higher dosages. To minimize the risk of dizziness and postural hypotension consequent to iloperidone's antagonism of a_1-adrenergic receptors, it is recommended that the medication be initiated at 1 mg orally twice daily and titrated upward with caution. Increases to reach the target dosage should not exceed 2 mg twice daily (e.g., 4 mg/day). Control of symptoms may be delayed during the first 1-2 weeks of treatment compared with other SGAs that do not require titration (Vanda Pharmaceuticals 2016). Clinical experience with iloperidone is accruing, as is comparative information on iloperidone in relation to other SGAs (Potkin *et al.* 2013; Rado and Janicak 2014; Tarazi and Stahl 2012). Additional clinical trials of iloperidone are ongoing (see www.clinicaltrials.gov).

Structure-Activity Relations and Pharmacological Profile

Iloperidone is an SGA of the piperidinyl-benzisoxazole class (Figure 32-1). Structurally similar benzisoxazole derivatives include risperidone and its metabolite paliperidone as well as ziprasidone. Iloperidone's chemistry and specific binding profile across multiple neuroreceptors are complex (Citrome 2010; Kalkman *et al.* 2003). In brief, similar to several other SGAs, iloperidone is a serotonin$_{2A}$ (5-HT$_{2A}$) and dopamine$_2$ (D$_2$) receptor antagonist. It has strong affinity for dopamine$_3$ (D$_3$) receptors and a lesser (but still more pronounced compared with other SGAs) affinity for dopamine$_4$ (D$_4$) receptors. It also has affinity for both serotonin$_6$ and serotonin$_7$ receptors. Iloperidone is further distinguished by its antagonism of a$_1$-adrenergic receptors. The strength of iloperidone's a$_1$-receptor affinity exceeds that of all other SGAs except clozapine. In contrast, iloperidone has low affinity for serotonin$_{1A}$ (5-HT$_{1A}$) and histamine$_1$ (H$_1$) receptors. Collectively, this constellation of receptor affinities may account for iloperidone's adverse effects of postural hypotension risk, prolactin-elevating capacity, modest propensity for weight gain, and mild sedative effects.

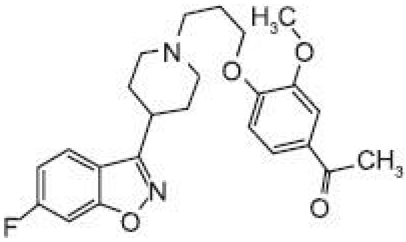

FIGURE 32-1. Chemical structure of iloperidone.

Pharmacokinetics and Disposition

Iloperidone is readily absorbed from the gastrointestinal tract and reaches peak plasma concentrations approximately 2 hours after ingestion. Its absorption is slowed by food, but its bioavailability is unaffected; thus, it can be given either with or without food.

Iloperidone is extensively metabolized by the cytochrome P450 (CYP) enzyme system, in particular the 3A4 and 2D6 isoenzymes. Iloperidone's average half-life in "regular" (extensive) CYP2D6 metabolizers is approximately 24 hours. Clinicians need to be cautious when prescribing iloperidone concurrently with agents that inhibit CYP2D6 and CYP3A4 enzymes, a category that includes several antidepressant medications. Iloperidone dosages should be reduced by one-half when administered in combination with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin). Similarly, when administered with a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine), iloperidone dosages should also be reduced (Vanda Pharmaceuticals 2016). It has been shown that a statistically significantly greater proportion of iloperidone responders than nonresponders have average plasma concentrations of [?] 5 ng/mL. That said, data on blood levels of iloperidone are not available for use in clinical practice (Weiden 2012). In studies performed in vitro, iloperidone at therapeutic concentrations decreased gene expression and protein activity of CYP3A4, a finding that supports potential clinically significant drug interactions between iloperidone and antidepressants, benzodiazepines, macrolide antibiotics, and other medications metabolized by CYP3A4 (Danek *et al.* 2020a, 2020b). Also, dosages should be reduced by one-half in individuals who are CYP2D6 poor metabolizers, which can be determined using available laboratory tests.

Iloperidone is currently available only in tablet form, with multiple tablet strengths to facilitate dosage titration (1, 2, 4, 6, 8, 10, and 12-mg tablets). No liquid or short-term intramuscular or long-acting injectable formulations of this agent have been developed.

There is currently no clinical evidence that the dosage of iloperidone requires adjustment on the basis of age or gender, although it is noteworthy that the potential for postural hypotension may be markedly higher in the elderly. Clinical studies of iloperidone in schizophrenia did not include sufficient numbers of patients age 65 years or older to determine whether older persons respond differently from younger adults. Among more than 3,000 patients treated with iloperidone in the early registration trials, only 25 patients (0.5%) were age 65 years or older, and there were no patients age 75 years or older. Iloperidone's safety and effectiveness in pediatric patients have not yet been well studied; therefore, the drug should not be prescribed to children or adolescents. In addition, iloperidone's teratogenic risk is unknown. It is therefore advised that lactating women who are being treated with iloperidone refrain from breastfeeding their newborns. The most recent FDA recommendations regarding the use of antipsychotics during pregnancy and the neonatal period also apply to iloperidone (see the FDA's MedWatch program at www.fda.gov/Safety/MedWatch); these guidelines note that third-trimester use of iloperidone may cause extrapyramidal and/or withdrawal symptoms in neonates.

Indications and Efficacy

Iloperidone is FDA approved for the acute treatment of schizophrenia. No other indications for iloperidone were under consideration by the FDA at the time of this writing. However, the clinical trials program for this drug now includes investigative studies of mood disorders that are currently ongoing (see www.clinicaltrials.gov).

Schizophrenia

Pivotal Clinical Trials

Iloperidone's FDA approval for the treatment of schizophrenia was predominantly based on four short-term placebo-controlled trials, highlighted in Table 32-1. In addition, two long-term trials have been published (Cutler *et al.* 2013; Kane *et al.* 2008). These studies are described in the following paragraphs. A more complete review of drug development and initial trials in humans is provided elsewhere (Citrome 2010; Rado and Janicak 2014).

TABLE 32-1. Pivotal clinical trials of iloperidone efficacy in patients with schizophrenia or schizoaffective disorder

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	***N* and diagnosis**	**Iloperidone and comparator drug dosages, mg/day**	**Efficacy outcome measure**	**Symptom change from baseline to endpoint**
Potkin *et al.* 2008 Three 6-week randomized, double-blind studies comparing ILO against PLA	1,943 patients with schizophrenia or schizoaffective disorder	*Study 1:* ILO 4, 8, 12; HAL 15; PLA	**Primary:** PANSS-T or PANSS-derived BPRS change from baseline to endpoint	*Study 1*

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

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Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint
		Study 2: ILO 4-8, 10-16; RIS 4-8; PLA	**Secondary:** PANSS-P, PANSS-N, PANSS-GP; BPRS change from baseline to each postbaseline assessment; CGI-S in Studies 2 and 3	* Changes in PANSS-T from baseline were significant with ILO 12 (*P* = 0.04) and HAL 15 (*P* < 0.01).
		Study 3: ILO 12-16, 20-24; RIS 6-8; PLA		* Changes with combined ILO 8 and ILO 12 groups were NS vs. PLA.

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint
				* Changes with HAL vs. PLA were significant (*P* < 0.001). *Studies 2 and 3* * All ILO dosages as well as RIS changed BPRS from baseline in Studies 2 and 3. * Compared with PLA,

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint
				changes were significant with ILO 4-8 (*P* = 0.012) and ILO 10-16 (*P* = 0.001) in Study 2 and ILO 20-24 (*P* = 0.01) in Study 3. * ILO 12-16 vs. PLA was NS in Study 3. * RIS vs. PLA was significant in all

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint
				studies ($P < 0.001$).
		* All ILO dosages improved each variable vs. PLA except ILO 4-8 for PANSS-N in Study 2.		
Potkin *et al.* 2008 Combined analysis of three studies	1,553 patients who remained in the studies at least 2 weeks	--	--	All ILO dosages as well as HAL and RIS were statistically significant vs. PLA ($P < 0.05$).

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	***N* and diagnosis**	**Iloperidone and comparator drug dosages, mg/day**	**Efficacy outcome measure**	**Symptom change from baseline to endpoint**

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint
Cutler *et al.* 2008 Four-week study, 1-week titration, 3-week double-blind treatment for acute exacerbation	593 patients with schizophrenia	ILO 24; ZIP 160; PLA	**Primary:** change from baseline on PANSS-T for ILO vs. PLA	ILO reduced PANSS-T significantly vs. PLA ($P < 0.01$).

Note: BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint
			Secondary: change from baseline on BPRS, PANSS-P, PANSS-N, PANSS-GP, CGI-S, CGI-C, CDSS	ILO and ZIP significantly reduced all measures except PANSS-GP.
				ILO reduced PANSS-P, CGI-S, and CGI-C significantly vs. PLA.
		Neither ILO nor ZIP		

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint
		reduced CDSS significantly.		

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	***N* and diagnosis**	**Iloperidone and comparator drug dosages, mg/day**	**Efficacy outcome measure**	**Symptom change from baseline to endpoint**
Kane *et al.* 2008 Long-term (46-week) double-blind maintenance phase after 6-week stabilization	473 patients with schizophrenia or schizoaffective disorder who had responded to ILO (*n* = 371) or HAL (*n* = 118) during the stabilization phase (36.6% responded to ILO and 37.8% responded to HAL in the acute phase)	ILO 4-16; HAL 5-20; mean dosage at end of maintenance was 12.5 for both drugs	**Primary:** time to relapse *	Difference in time to relapse between ILO (89.8 days) and HAL (101.8 days) was not significant.
			Secondary: change from baseline to endpoint on PANSS, BPRS, and CGI-C	Relapse rate was 43.5% for ILO vs. 41.2% for HAL.
		Both groups improved;		

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Study	*N* and diagnosis	Iloperidone and comparator drug dosages, mg/day	Efficacy outcome measure	Symptom change from baseline to endpoint
		PANSS scores were not significantly different at endpoint between ILO and HAL.		

Note. BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CGI-C = CGI-Change; CGI-S = CGI-Severity; HAL = haloperidol; ILO = iloperidone; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; PANSS-GP = PANSS-General Psychopathology; PANSS-N = PANSS-Negative Symptoms; PANSS-P = PANSS-Positive Symptoms; PANSS-T = PANSS total; PLA = placebo; RIS = risperidone; ZIP = ziprasidone.

* Relapse = [?] 25% increase in PANSS-T scores; discontinuation due to lack of efficacy, hospitalization, or CGI increase of 2 points.

Potkin *et al.* (2008) reviewed the 6-week double-blind period of the pivotal trials that evaluated iloperidone's efficacy in the treatment of schizophrenia. All of these trials included screening, an acute double-blind phase, and a long-term maintenance phase.

Study 1 enrolled patients ages 18-65 years with acute or subacute exacerbations of schizophrenia or schizoaffective disorder and with Positive and Negative Syndrome Scale (PANSS) scores [?] 60. A total of 121 patients were randomly assigned to receive iloperidone 4 mg/day, 125 to iloperidone 8 mg/day, 124 to iloperidone 24 mg/day, 124 to haloperidol 15 mg/day, and 127 to placebo. After a screening and a 3-day placebo run-in period as well as a 7-day fixed-titration period, patients received study medication for 5 weeks. The primary objective was to determine the efficacy of iloperidone versus placebo. The primary efficacy variable was change in the PANSS total score (PANSS-T) from baseline to endpoint (day 42 or last visit before discontinuation). Although PANSS-T scores improved significantly from baseline for the iloperidone 12 mg/day ($P = 0.047$) and the haloperidol ($P < 0.001$) groups, improvement for the combined iloperidone 8 mg/day and 12 mg/day group was not significantly different from that for the placebo group. The all-cause discontinuation rates were 57%, 64%, and 58% for iloperidone 4 mg/day, 8 mg/day, and 12 mg/day, respectively; 65% for haloperidol; and 69% for placebo (Potkin *et al.* 2008).

In Study 2, patients selected according to the same inclusion criteria used in Study 1 were randomly assigned to receive iloperidone 4-8 mg/day ($n = 53$; 52% discontinued the study before endpoint) or 10-16 mg/day ($n = 154$; 44% discontinued), risperidone 4-8 mg/day ($n = 153$; 42% discontinued), or placebo ($n = 156$; 60% discontinued). The primary objective was again to determine the efficacy of iloperidone versus placebo. Both dosage ranges of iloperidone resulted in significantly greater symptom improvement (as measured by Brief Psychiatric Rating Scale scores) from baseline compared with placebo (Potkin *et al.* 2008).

In Study 3, patients selected according to the previously described criteria were randomly assigned to receive iloperidone 12-16 mg/day ($n = 244$; 46% discontinued) or 20-24 mg/day ($n = 145$; 41% discontinued), risperidone 6-8 mg/day ($n = 157$; 29% discontinued), or placebo ($n = 160$; 46% discontinued). In this study, the iloperidone 12-16 mg/day dosage failed to separate from placebo (Potkin *et al.* 2008).

A combined analysis of all three studies was performed to eliminate the impact of early discontinuations (i.e., those occurring in the initial 2 weeks of the studies, during which the drug reaches steady state). When the analysis was restricted to patients who had remained in double-blind treatment for at least 2 weeks ($n = 1,553$), it showed that each of the iloperidone dosage ranges (4-8, 10-16, and 20-24 mg/day) separated significantly from placebo (Potkin *et al.* 2008).

A 4-week double-blind study (Cutler *et al.* 2008) evaluated the efficacy of iloperidone 24 mg/day against that of placebo and of ziprasidone 160 mg/day in patients with acute exacerbation of schizophrenia by measuring change from baseline in the PANSS-T score and the PANSS positive, negative, and general psychopathology scale scores; the Calgary Depression Scale for Schizophrenia (CDSS) score; and the Clinical Global Impression--Severity (CGI-S) score. Patients receiving iloperidone showed significantly greater reductions on PANSS-T scores at 4 weeks compared with those receiving placebo. Although both iloperidone and ziprasidone produced significantly greater improvement on PANSS negative and positive and CGI-S scores compared with placebo, none of the drugs produced significant improvement on PANSS general psychopathology scores, nor did any drug affect CDSS scores.

Kane *et al.* (2008) conducted a long-term efficacy analysis using data from patients who had completed the 6-week double-blind phase of the three pivotal studies described previously. Patients who had at least a 20% reduction in PANSS-T scores and a CGI score of less than 4 and who had received at least one dose of long-term-phase medication were randomly assigned to iloperidone or haloperidol for 48 weeks of double-blind maintenance treatment (mean dosage at endpoint was 12.5 mg/day for both drugs). The primary efficacy variable was relapse (defined as an increase of [?] 25% in the PANSS score). Differences between the iloperidone group and the haloperidol group in time to relapse were not significant--63.6% of patients in both groups completed the long-term phase of the trial.

Cutler *et al.* (2013) reported on a 25-week open-label extension study. More than 58% of patients discontinued iloperidone. Overall improvement was seen in 80% of patients.

Weiden *et al.* (2014) reported on a 12-week trial in which patients with schizophrenia who were taking risperidone, olanzapine, or aripiprazole but were experiencing problems with tolerability or efficacy were switched to iloperidone ([?] 12 mg twice daily) via random assignment to either immediate cessation of the original drug or gradual down-titration. The results were similar across all groups, and the two switching strategies yielded comparable efficacy and tolerability.

A 24-week study of iloperidone (Weiden *et al.* 2016) demonstrated its efficacy as a maintenance treatment for schizophrenia, with a reduction in relapse with typical treatment dosages between 12 mg/day and 20 mg/day. A review of the relative potency and dose equivalency of iloperidone dosages suggested that 20 mg/day of iloperidone represents the 95% effective dose of this drug (Leucht *et al.* 2020). Dose equivalency to 1 mg/day of risperidone was estimated at 3.22 mg/day of iloperidone. In a systematic review and network meta-analysis of placebo-controlled and head-to-head randomized controlled trials of antipsychotic drugs, iloperidone was found to induce moderate change in positive symptoms and minimal change in negative symptoms for people with schizophrenia (Huhn *et al.* 2019).

Pharmacogenetic Studies

Clinical trials of iloperidone have sought to establish the drug's pharmacogenetic characteristics (Volpi *et al.* 2009a, 2009b) by exploring the relationship between its efficacy and various candidate genes related to dopamine receptors, dopamine b-hydroxylase, the serotonin$_{1B}$ receptor, and ciliary neurotrophic factor (CNTF). CNTF is a cytokine in the interleukin 6 cytokine family that suppresses noradrenergic and serotonergic function (Galter and Unsicker 1999). A null mutation in *CNTF* leads to a non-G/G rs1800169 genotype that cannot produce a functional protein and has been linked to an increased risk of psychosis (Thome *et al.* 1996). However, a meta-analysis involving more than 1,000 patients and a similar number of control subjects (Lin and Tsai 2004) found no association between *CNTF* and schizophrenia risk.

In a 4-week randomized, placebo-controlled study in 417 patients genotyped for *CNTF*, 279 patients received iloperidone and 138 received placebo (Lavedan *et al.* 2008). Iloperidone produced significantly greater improvement on symptom scores versus placebo in patients with an active

CNTF gene, whereas patients with the CNTF null allele showed no greater response to iloperidone than to placebo.

In a whole-genome study of 407 patients from the same sample, of whom 218 patients received iloperidone, six single-nucleotide polymorphisms (SNPs) associated with iloperidone efficacy were identified (Volpi *et al.* 2009b). The identified loci included SNPs of the neuronal PAS domain protein 3 gene (*NPAS3*); of the XK, Kell blood group complex subunit-related family, member 4 gene (*XKR4*); of the tenascin-R gene (*TNR*); of the glutamate receptor, ionotropic, AMPA 4 gene (*GRIA4*); of the glial cell line-derived neurotrophic factor receptor alpha 2 gene (*GFRA2*); and of the nudix hydrolase 9 pseudogene 1 (*NUDT9P1*) located in the chromosomal region of the serotonin receptor 7 gene (*HTR7*). More than 75% of the iloperidone-treated patients in the group with the optimal genotype combinations showed [?] 20% symptom improvement, whereas only 37% of patients with other genotypes showed [?] 20% improvement.

Another whole-genome association study (Volpi *et al.* 2009a) was conducted in 183 patients with schizophrenia who received an electrocardiogram on day 14 of treatment with iloperidone, after the drug had reached steady state. DNA polymorphisms associated with QT prolongation were found in six loci, including *CERKL*, thought to be part of the ceramide pathway; *SLCO3A1*, which encodes organic anion-transporting polypeptides; various genes involved in myocardial infarction (*PALLD*), cardiac structure and function (*BRUNOL4*), and cardiac development (*NRG3*); and an SNP on *NUBPL* with unknown function. Each SNP defined two genotype groups associated with a low mean QT interval change or a higher mean QT interval prolongation.

Although these findings have attracted considerable interest from the field, pharmacogenomic approaches to drug optimization need to be tested further in larger studies before these findings can be of clinical use. Nevertheless, the incorporation of pharmacogenetic testing into the regulatory registration trials of this drug represents an important new aspect of psychopharmacological drug development.

Other Indications

Little information is available on the use of iloperidone in patients with first-episode psychosis. Similarly, there are no studies to inform the use of iloperidone in patients with treatment-refractory schizophrenia. There is no information on the efficacy or tolerability of iloperidone in patients with comorbid substance use disorders. Information on the use of iloperidone to treat other comorbid conditions and/or other primary psychiatric and neuropsychiatric disorders is scant. An open-label pilot study of iloperidone given over 5 months to patients with bipolar disorder with mixed features showed efficacy in treating mood symptoms, both manic and depressive (Singh *et al.* 2017). Given the paucity of data to guide treatment, off-label use of this drug cannot be recommended.

Side Effects and Toxicology

Common Adverse Events in Early Studies

The safety of iloperidone in short-term studies was examined in a pooled analysis of the three 6-week Phase II studies of acute schizophrenia ($N =$ 1,943) conducted between 1998 and 2002 (Potkin *et al.* 2008). A total of 1,912 patients received at least one dose of study medication and were included in this pooled analysis. The safety cohort included 440 patients taking placebo, 463 taking iloperidone 4-8 mg/day, 456 taking iloperidone 10-16 mg/day, 125 taking iloperidone 20-24 mg/day, 118 taking haloperidol 15 mg/day, and 306 taking risperidone 4-8 mg/day. The most common treatment-related adverse events associated with iloperidone across all three dosage groups were dizziness, dry mouth, somnolence, and dyspepsia (Table 32-2).

TABLE 32-2. Safety profile of iloperidone in short-and long-term studies: adverse events

occurring in at least 5% of patients in any active-treatment group

Event (%)	Short-term studies[a]					Long-term studies[b]	
	ILO 4-8 mg/day (*n* = 463)	ILO 10-16 mg/day (*n* = 456)	ILO 20-24 mg/day (*n* = 125)	HAL 15 mg/day (*n* = 118)	RIS 4-8 mg/day (*n* = 306)	ILO (*n* = 371)	HAL (*n* = 118)
Akathisia	3.7	1.5	4.8	13.6	6.9	3.8	14.4
Dizziness	12.1	10.3	23.2	5.1	7.2	5.1	4.2
EPS	5.4	4.8	4.0	20.3	9.5	0.8	5.9
Tremor	2.8	2.6	4.8	22.0	6.9	4.9	12.7
Dry mouth	5.2	7.9	10.4	2.5	2.9	*	*
Dyspepsia	7.8	5.5	4.8	11.0	5.9	*	*
Dystonia	0.9	0.9	0.8	11.9	2.6	*	*
Fatigue	4.3	4.6	6.4	7.6	1.6	*	*
Flatulence	1.9	1.3	1.6	5.1	2.3	*	*

Note. "Schizophrenia aggravated" and "psychosis aggravated" were listed as adverse events in the Kane *et al.* 2008 study but were not included in this table. EPS = extrapyramidal side effects; HAL = haloperidol; ILO = iloperidone; RIS = risperidone.

* Did not occur in at least 5% of comparators.

[a] Pooled analysis of 6-week studies.

[b] Long-term (46 weeks) maintenance treatment (mean dosage at study end was 12.5 mg/day for both drugs).

Source. Adapted from Kane *et al.* 2008 and Weiden *et al.* 2008.

Event (%)	Short-term studies[a]					Long-term studies[b]	
	ILO 4-8 mg/day (*n* = 463)	**ILO 10-16 mg/day (*n* = 456)**	**ILO 20-24 mg/day (*n* = 125)**	**HAL 15 mg/day (*n* = 118)**	**RIS 4-8 mg/day (*n* = 306)**	**ILO (*n* = 371)**	**HAL (*n* = 118)**
Nasal congestion	4.8	5.0	5.6	1.7	2.6	*	*
Somnolence	5.0	5.7	8.0	6.8	5.9	*	*
Insomnia	*	*	*	*	*	18.1	16.9
Anxiety	*	*	*	*	*	10.8	11.0
Headache	*	*	*	*	*	6.2	4.2
Agitation	*	*	*	*	*	5.7	5.1
Muscle rigidity	*	*	*	*	*	4.0	12.7

Note. "Schizophrenia aggravated" and "psychosis aggravated" were listed as adverse events in the Kane *et al.* 2008 study but were not included in this table. EPS = extrapyramidal side effects; HAL = haloperidol; ILO = iloperidone; RIS = risperidone.

* Did not occur in at least 5% of comparators.

[a] Pooled analysis of 6-week studies.

[b] Long-term (46 weeks) maintenance treatment (mean dosage at study end was 12.5 mg/day for both drugs).

Source. Adapted from Kane *et al.* 2008 and Weiden *et al.* 2008.

	Short-term studies[a]					Long-term studies[b]	
Event (%)	**ILO 4-8 mg/day (*n* = 463)**	**ILO 10-16 mg/day (*n* = 456)**	**ILO 20-24 mg/day (*n* = 125)**	**HAL 15 mg/day (*n* = 118)**	**RIS 4-8 mg/day (*n* = 306)**	**ILO (*n* = 371)**	**HAL (*n* = 118)**
Restlessness	*	*	*	*	*	3.5	6.8
Constipation	*	*	*	*	*	2.2	5.1

Note. "Schizophrenia aggravated" and "psychosis aggravated" were listed as adverse events in the Kane *et al.* 2008 study but were not included in this table. EPS = extrapyramidal side effects; HAL = haloperidol; ILO = iloperidone; RIS = risperidone.

* Did not occur in at least 5% of comparators.

[a] Pooled analysis of 6-week studies.

[b] Long-term (46 weeks) maintenance treatment (mean dosage at study end was 12.5 mg/day for both drugs).

Source. Adapted from Kane *et al.* 2008 and Weiden *et al.* 2008.

With respect to available data from long-term studies, three prospective multicenter studies--each with a 6-week stabilization period followed by a 46-week double-blind maintenance phase--inform understanding of iloperidone's longer-term tolerability (Kane *et al.* 2008; see Table 32-2). Patients were randomly assigned to receive either iloperidone 4-16 mg/day or haloperidol 5-20 mg/day. Among the 1,644 patients who underwent random assignment and the 1,326 who completed the 6-week stabilization period, 473 (iloperidone: 359, haloperidol: 114) were included in the long-term efficacy analysis and 489 (iloperidone: 371, haloperidol: 118) were included in the safety analysis. The most common adverse events reported for iloperidone were insomnia, anxiety, and headache.

Extrapyramidal Side Effects

In a pooled analysis of pivotal short-term trials comparing iloperidone (4-8 mg/day, 10-16 mg/day, and 20-24 mg/day), risperidone, and haloperidol, all iloperidone dosages demonstrated significant improvement (as measured by overall EPS ratings from baseline to endpoint on the Extrapyramidal Symptom Rating Scale [ESRS] [Chouinard and Margolese 2005]). By comparison, there was no significant change with risperidone and significant worsening with haloperidol. Akathisia items on the ESRS all showed significant improvement from baseline for iloperidone at the 10-16 mg/day and 20-24 mg/day dosage ranges (Nair *et al.* 2020; Weiden *et al.* 2008). The low EPS profile of iloperidone is an advantage clinically, even in this era of prescribing predominantly SGAs, in which one's risk of EPS is much lower than in the past (Weiden 2012). Moreover, the absence of a dose-related increase in EPS across dosage ranges in clinical trials of iloperidone is conspicuous and encouraging.

Orthostatic Hypotension

In view of its antagonism of a_1-adrenergic receptors, iloperidone possesses the potential for autonomic side effects. In its clinical trials program, iloperidone was associated with decreases in supine and standing systolic and diastolic blood pressure in all dosage groups. Decreases in blood pressure were mostly observed within the first week of treatment and were generally not sustained. Orthostatic hypotension was observed more frequently in all active-treatment groups (iloperidone, risperidone, and haloperidol) than in the placebo group. Sustained orthostatic hypotension was observed in 0.4% ($n = 2$), 3.8% ($n = 17$), and 4.8% ($n = 6$) of patients receiving iloperidone 4-8 mg/day, 10-16 mg/day, and 20-24 mg/day, respectively. According to the manufacturer's full prescribing information (Vanda Pharmaceuticals 2016), iloperidone must be initiated slowly and gradually so as to avoid orthostatic hypotension, with a starting dosage of 1 mg twice daily, increasing to 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively, to a target dosage range of 12-24 mg/day. Clinicians should therefore pay particular attention to dizziness early in treatment with iloperidone. It is also important to go even slower with initial titration in patients who may be at risk for postural hypotension (Weiden 2012).

Weight Gain and Metabolic Effects

One of the potential advantages of iloperidone could be its profile with respect to metabolic issues and weight gain (De Hert *et al.* 2012; Tarazi and Stahl 2012). Compared with patients receiving placebo, patients receiving iloperidone exhibited a small but statistically significant increase in weight across all dosages. For all patients completing the respective studies, the mean weight gain was 2.4 kg in each iloperidone dosing group. Clinically significant weight gain (defined as a [?] 7% increase in body weight from baseline) occurred in 12.3% of subjects in all iloperidone groups (Weiden *et al.* 2008). The majority of the weight gain occurred within the first 6 weeks of the studies (6.4%). Long-term treatment with iloperidone also produced slight increases in total cholesterol, triglycerides, and glucose levels (Kane *et al.* 2008). Increased prolactin levels were not observed in the pooled analysis of the three 6-week trials. The prescribing information (Vanda Pharmaceuticals 2016), however, emphasizes findings from the 4-week iloperidone versus ziprasidone versus placebo trial, in which 26% of subjects receiving iloperidone, versus 12% of those receiving placebo, exhibited elevated plasma prolactin levels. Thus, the relatively more favorable weight and metabolic profiles of iloperidone constitute a distinction that might guide the selection and use of iloperidone in particular patient groups (Weiden 2012).

However, in a provocative preclinical study in which rats were exposed to iloperidone, asenapine, or olanzapine (Boyda *et al.* 2013), the iloperidone-exposed rats developed glucose intolerance. In a double-blind study in which healthy human volunteers were randomly assigned to receive olanzapine, iloperidone, or placebo for 1 month, iloperidone and placebo did not induce any significant weight gain, lipid elevation, or alteration in insulin metabolism compared with olanzapine (Ballon *et al.*

2018). In a retrospective study, 64 outpatients treated with iloperidone for a mean of 236 days had significant within-group weight gain at 12 weeks (4.54 lb [2.06 kg]; $P < 0.01$) and up to 1 year (5.13 lb [2.33 kg]; $P = 0.02$) compared with olanzapine, which yielded an average weight gain of 10.3 lb (4.67 kg; ($P < 0.01$) following treatment up to 1 year (Greger *et al.* 2021).

QT Interval Prolongation

With respect to potentially life-threatening side effects, there was evidence of significant QT/QTc interval prolongation across all iloperidone groups in the drug's pivotal study program, and this potential drug effect was a focus of a review by the FDA. Specifically, the least squares mean change in QTc interval from baseline to endpoint in these studies was 2.9 milliseconds, 3.9 milliseconds, and 9.1 milliseconds for iloperidone 4-8 mg/day, 10-16 mg/day, and 20-24 mg/day, respectively. It is noteworthy that no deaths or serious arrhythmias attributable to QT prolongation occurred in these studies (Weiden 2012; Weiden *et al.* 2008). Potkin *et al.* (2013) examined the incidence of QTc prolongation in patients randomly assigned to receive iloperidone, quetiapine, or ziprasidone. To further test for metabolic inhibition, there was a period of coadministration of paroxetine and paroxetine plus ketoconazole. These conditions resulted in QTc intervals of 60 milliseconds or greater in approximately 10% of patients receiving iloperidone. However, no patients had clinical symptoms, and none had a QTc interval that reached or exceeded 500 milliseconds. The mechanism of QT/QTc interval prolongation by antipsychotic drugs is attributed to blockade of the human ether-a-go-go-related gene (*hERG*), which encodes a subunit of the potassium ion channel (Silvestre and Prous 2007). Vigneault *et al.* (2012) demonstrated that iloperidone blocks *hERG*, resulting in a 42.7-millisecond QT interval prolongation after administration of a single oral dose in guinea pigs. Lee *et al.* (2021) further studied the effect of iloperidone on *hERG* 1A/3.1 (a K^+ channel specific to primates) and found that iloperidone inhibits *hERG* 1A/3.1 currents by binding to the open states of the channels but does not disrupt the membrane trafficking or the surface membrane expression of *hERG* 1A channel protein. Further research is needed to translate these findings to clinical practice.

Contraindications

According to the manufacturer's prescribing information (Vanda Pharmaceuticals 2016), iloperidone should be avoided in combination with other drugs that are known to prolong the QTc interval, a group that includes Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications, and antibiotics. This prohibition makes sense, given iloperidone's metabolism through these cytochrome pathways. In addition, it is recommended that iloperidone be avoided in persons with congenital long QT syndrome or cardiac arrhythmias.

Like all other SGAs, iloperidone carries a black box warning regarding the increased mortality risk associated with the use of antipsychotic drugs in elderly patients with dementia-related psychosis. That said, iloperidone is not approved for the treatment of patients with dementia-related psychosis, and its use in the elderly should be avoided pending future clinical trials.

Conclusion

Iloperidone is an FDA-approved antipsychotic with proven efficacy in the treatment of schizophrenia. Recent reviews suggest that it may be less efficacious than other SGAs for treating schizophrenia. In a systematic review and network meta-analysis of placebo-controlled and head-to-head randomized controlled trials of antipsychotic drugs, iloperidone was found to induce moderate change in positive symptoms and minimal change in negative symptoms for people with schizophrenia (Huhn *et al.* 2019). However, there are insufficient data at present to substantiate this viewpoint. The current lack of short-term intramuscular and long-acting intramuscular formulations also limits the broader applicability of this medication in clinical practice. That said, its side-effect profile could perhaps favor preferential use in patients who experience weight gain from other antipsychotics. Its use to treat mood disorders and other conditions is not FDA approved, and clinical studies are under way in such areas.

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CHAPTER 33

Lurasidone

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Lurasidone (Latuda) is a more than 10-year-old addition to the atypical antipsychotic class. It received FDA approval for the treatment of schizophrenia in October 2010 and is currently approved for the treatment of adults and adolescents (ages 13-17 years). In June 2013, lurasidone also received FDA approval for the treatment of bipolar depression in adults as an adjunctive therapy with lithium or valproate. Lurasidone now has an approved indication for monotherapy treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) in adults and pediatric patients (ages 10-17 years).

Like all currently registered antipsychotic medications, lurasidone is a dopamine$_2$ (D_2) receptor antagonist. In addition, this compound is a full antagonist at the serotonin$_{2A}$ (5-HT_{2A}) receptor, similar to many other atypical antipsychotic medications. Lurasidone has other receptor affinities that may contribute to additional beneficial or adverse effects. Because lurasidone is newer than medications such as risperidone or olanzapine, its comparative literature is more limited than that of other medications, although lurasidone's approved indication for bipolar depression has led to published research in adults with bipolar depression as well as research examining lurasidone's efficacy and safety in children with schizophrenia or bipolar disorder. A current interesting line of investigation, with benefits for children and adolescents, is lurasidone's potential utility in the treatment of bipolar depression with mixed (subsyndromal hypomanic) features.

In this chapter, I review the pharmacological properties and efficacy basis of lurasidone, the side effects and adverse events seen in pivotal critical follow-up studies, and other features of the compound that may prove to be important in clinical applications of this agent. I also consider the question of what seems unique about lurasidone compared with other available antipsychotic medications.

Structure-Activity Relations and Pharmacological Properties

Receptor Binding Profile

Lurasidone belongs to the chemical class of benzisothiazole derivatives (Figure 33-1). The compound is a full antagonist at D_2 and 5-HT_{2A} receptors, a profile it shares with other atypical antipsychotics. Lurasidone also has high affinity for $serotonin_7$ (5-HT_7) receptors, with in vitro affinity for 5-HT_7 being relatively higher than that shown by the drug for D_2 and 5-HT_{2A} receptors. Lurasidone is a partial agonist at $serotonin_{1A}$ (5-HT_{1A}) receptors (Ishibashi *et al.* 2010) and has moderate affinity for noradrenergic receptors. Lurasidone's minimal affinity for a_1-adrenergic receptors would be expected to convey a reduced risk for orthostatic hypotension in comparison with compounds that have higher affinity for this receptor. Lurasidone appears to have weak affinity for $serotonin_{2C}$ receptors and no affinity for $histamine_1$ receptors, a profile that should carry relatively low risk for weight gain. Lurasidone lacks affinity for muscarinic acetylcholine M_1 receptors, which suggests reduced risk for cholinergic cognitive deficits and other side effects.

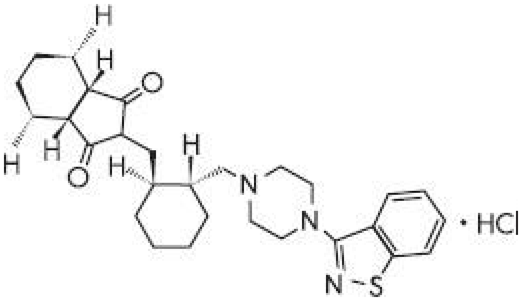

FIGURE 33-1. Chemical structure of lurasidone.

Pharmacokinetics and Dosing

Lurasidone is rapidly absorbed and reaches peak concentrations within 3 hours for the lowest effective antipsychotic dose, 40 mg. Steady state is reached within 7 days (Sunovion Pharmaceuticals 2013). The pharmacokinetics of lurasidone are dose proportional within a total daily dosage of 20-160 mg. The molecule is metabolized in the liver via the cytochrome P450 (CYP) 3A4 enzyme system, which leads to the conclusion that lurasidone should not be used in the presence of strong inducers (e.g., rifampin) or inhibitors (e.g., ketoconazole) of CYP3A4. Lurasidone does show a food effect. A study examining food effects on lurasidone concentrations found that taking the drug with meals containing 350 calories or more, with either low or high fat content, led to a doubling of the bioavailability of lurasidone compared with dosing during fasting (Chiu *et al.* 2010).

The recommended starting dosage of lurasidone is 40 mg/day, with the dose taken concurrently with at least 350 calories of food. Dosages up to 160 mg/day in adults and up to 80 mg/day in adolescents are currently approved for treatment of schizophrenia,

and dosages up to 120 mg/day in adults and up to 80 mg/day in pediatric patients are approved for bipolar depression. As previously noted, lurasidone should not be used by patients taking medications that are strong metabolic inducers or inhibitors of CYP3A4. Dosage adjustment is recommended if lurasidone is administered with a moderate CYP3A4 inhibitor. Also, grapefruit and grapefruit juice should be avoided by individuals taking lurasidone. There are no suggested dosage adjustments based on gender, ethnicity, or smoking. In individuals with moderate to severe renal impairment, the recommended starting dosage is 20 mg/day, and dosages should not exceed 80 mg/day. For those with moderate to severe hepatic impairment, the recommended starting dosage is also 20 mg/day, with a maximum dosage of 40 mg/day for moderate hepatic impairment and 80 mg/day for severe impairment. Lurasidone is currently available in 20-, 40-, 60-, 80-, and 120-mg tablets (Sunovion Pharmaceuticals 2013). In a study examining the effects of different lurasidone dosages among hospitalized patients with acute schizophrenia, lurasidone 20 mg/day failed to separate from placebo (Loebel *et al.* 2016).

Lurasidone lacks a requirement for initial dosage titration and appears to require minimal adjustment and tinkering. Having a starting dose with substantial efficacy is a strong point for many patients. Food effects are an issue, given that optimal exposure requires the medication to be taken with at least 350 calories of food (with no minimum fat content specified); however, the lack of a need for titration and the uncomplicated requirements for suitable meals make it easier to apply this treatment to patients who may be challenged in their ability to adhere to complex regimens.

Efficacy and Tolerability

Pivotal Registration Trials in Schizophrenia

In the standard drug development program, lurasidone at daily dosages of 40 mg, 80 mg, and 120 mg was compared with placebo in four separate studies (Meltzer *et al.* 2011; Nakamura *et al.* 2009; Nasrallah *et al.* 2013; Ogasa *et al.* 2013), with several different dosing and comparator strategies. A fifth study (Loebel *et al.* 2013) added a 160-mg/day dosage. Citrome (2011a, 2011b) reviewed data based on conference presentations for the schizophrenia development program. Patients ranged in age from 18 to 74 years and were symptomatic with an acute exacerbation of psychosis. In the early clinical studies, the dosage that most consistently separated from placebo was 80 mg/day, although 40 mg/day and 120 mg/day did as well in some trials.

Comparative Efficacy Studies

Schizophrenia

Four blinded and randomized studies compared lurasidone with other agents in the treatment of schizophrenia. In the first study (Potkin *et al.* 2011), lurasidone was compared with ziprasidone in a 3-week randomized trial in 301 patients with schizophrenia. Both treatments improved symptoms as measured by the Positive and Negative Syndrome Scale (PANSS), and there were no significant differences in endpoint PANSS scores.

In the second study (Meltzer *et al.* 2011), lurasidone was compared with olanzapine in clinically unstable patients with schizophrenia who had been admitted to inpatient care. Both olanzapine and lurasidone were superior to placebo for clinical response. In addition, weight gain was significantly greater with olanzapine than with either lurasidone or placebo, whereas rates of akathisia were significantly higher in the lurasidone group compared with the other two groups.

In the third study (Loebel *et al.* 2013), two dosages of lurasidone (80 mg/day and 160 mg/day) were compared with quetiapine extended release (XR) 600 mg/day and placebo in inpatients experiencing an acute exacerbation of schizophrenia. Both lurasidone (at both dosages) and quetiapine separated from placebo, and weight gain and sedation/sleepiness were more frequent with quetiapine than with either dosage of lurasidone.

In the fourth study (Citrome *et al.* 2012), clinically stable patients with schizophrenia were randomly assigned to receive either risperidone or lurasidone and were followed for 12 months to assess potential differences in long-term safety. Findings included greater weight gain with risperidone, minimal differences between lurasidone and risperidone in efficacy, and no differences between the two agents in relapse rates. All-cause discontinuation rates were higher for lurasidone, possibly because of slight elevations in nausea in the lurasidone group.

Bipolar Depression

Two randomized, placebo-controlled trials of lurasidone were conducted in patients with bipolar depression. In the first study (Loebel *et al.* 2014b [monotherapy]), lurasidone at two different dosage ranges (20-60 mg/day and 80-120 mg/day) was compared with placebo. Both dosage ranges separated from placebo, with similar effect sizes. In the second study (Loebel *et al.* 2014a [adjunctive therapy]), lurasidone 20-120 mg/day was added to stable treatment with either valproate or lithium. Statistically significant separation from placebo was found. Lurasidone treatment was administered at a mean modal dosage of 75 mg/day, which translates to an available dosage of 80 mg/day. The results of these two studies led to lurasidone's approval by the FDA for both augmentation of lithium or valproate therapy and monotherapy of bipolar depression in June 2013.

In an additional post hoc analysis of the results of the monotherapy study, McIntyre *et al.* (2015) reported that lurasidone was effective in the treatment of a newly introduced DSM-5 (American Psychiatric Association 2013) entity--the specifier "with mixed features," which can be applied to depressive and bipolar disorders. In this study, the presence of mixed (subsyndromal hypomanic) features was defined as a Young Mania Rating Scale (Young *et al.* 1978) score of 4 or greater at study baseline. Fifty-six percent of the patients in the study (272 of 485) were identified as having depression with mixed features. Among the patients with mixed features, 182 received lurasidone (active treatment) and 90 received placebo. Lurasidone's efficacy in treating depression in patients with and without mixed features was essentially equivalent: 15.7-point decreases in Montgomery-Asberg Depression Rating Scale (Montgomery and Asberg 1979) scores were seen for patients without mixed features, and 15.2-point decreases were found for those with mixed features. Among patients who received active treatment, 82% of those without mixed features completed the trial, compared with 73% of those with mixed features. These data indicate that the presence of mixed features in bipolar depression should not be viewed as a contraindication to treatment with lurasidone.

In a study targeted at depression with mixed features, patients selected for the presence of major depressive disorder as defined in DSM-IV-TR (American Psychiatric Association 2000) and two or three manic symptoms were randomly assigned to receive lurasidone (n = 109) or placebo (n = 100) for a 6-week trial (Suppes *et al.* 2016). Lurasidone was superior to placebo, leading to a 20.5-point change in score on the Montgomery-Asberg Depression Rating Scale for active treatment compared with a 13-point change for placebo ($P < 0.001$; effect size $d = 0.80$). Completion rates were similar for active treatment and placebo (94% and 85%, respectively), and the remission rate was 49% for active treatment. Switch into mania did not occur with lurasidone treatment, and patients who received lurasidone manifested a 7-point decrease in their Young Mania Rating Scale scores. These data suggest efficacy for lurasidone in the treatment of major depressive disorder with mixed features as well as bipolar depression.

Efficacy in Children and Adolescents

Several studies have examined the safety and efficacy of lurasidone in children and adolescents with the conditions for which the drug is approved to treat adults. Goldman *et al.* (2017) reported on a three-arm efficacy study of participants with schizophrenia ages 13-17 (N = 327). Lurasidone at dosages of 40 mg/day or 80 mg/day was compared with placebo. Both dosages separated from placebo, with effect sizes of d = 0.48 or better on PANSS total scores. Safety outcomes were comparable to those in adults with schizophrenia, in that weight gain was < 0.50 kg for the 80 mg/day group. Only one participant discontinued because of akathisia. A 2-year open-label follow-up of these participants (Correll *et al.* 2022) found that the mean changes in weight from the double-blind baseline at week 52 and week 104 were + 3.3 kg and + 4.9 kg, respectively, compared with an expected weight gain of + 3.4 kg and + 5.7 kg (based on Centers for Disease Control and Prevention [CDC] sex-and age-matched normative data).

DelBello *et al.* (2017) evaluated the efficacy and safety of lurasidone (20-80 mg/day) versus placebo among 10-to 17-year-olds with a bipolar I disorder diagnosis who were experiencing a major depressive episode. Children's Depression Rating Scale scores of patients in the active treatment group separated from scores in the placebo group starting at week 2 of the 6-week treatment trial. Symptoms related to extrapyramidal side effects (EPS) did not differ markedly between the groups, and rates of switching into mania were essentially identical across the samples (6.9% [lurasidone] vs. 7.0% [placebo]). Finally, short-term weight gain was minimal in the study, with an average gain of 0.74 kg in the lurasidone group and 0.44 kg in the placebo group.

A 2-year open-label follow-up (DelBello *et al.* 2021) of the participants in the 2017 study revealed continued clinical improvement and, again, very modest weight gain: the mean changes in weight from the double-blind baseline were + 4.25 kg at week 52 (vs. expected weight gain of + 3.76 kg [based on CDC sex-and age-matched normative data]) and + 6.75 kg at week 104 (vs. expected weight gain of + 6.67 kg). Changes in depression scores from the open-label baseline were [?]13.4 at week 52 and [?]16.4 at week 104 ([?]11.3 at last-observation-carried-forward endpoint). Only 10% of participants discontinued treatment because of an adverse event.

Summary of Efficacy and Tolerability Data

The risk-benefit evaluation for lurasidone suggests a lower potential for metabolic consequences and QTc prolongation combined with a slightly higher risk of EPS and akathisia compared with some of the other atypical antipsychotic medications. Prolactin elevation appears to be minimal within the approved dosage range. Given the limited clinical experience with lurasidone, it may be premature to target an optimal patient for this medication; however, the reduced metabolic consequences of lurasidone would seem to be a very strong point. Patients who are extraordinarily vulnerable to EPS may require close monitoring.

Lurasidone's efficacy in treating schizophrenia relative to other agents was examined in four active comparison studies (Citrome *et al.* 2012; Loebel *et al.* 2013; Meltzer *et al.* 2011; Potkin *et al.* 2011), none of which found lurasidone to be inferior. It is not yet possible to assess lurasidone's relative efficacy in treating bipolar depression, given the absence of comparative trials to date. However, these four active comparison studies showed that lurasidone was at least as effective as placebo in treating children and adolescents with schizophrenia or bipolar depression, and that lurasidone's weight gain parameters in pediatric populations were very similar to those in adults.

Side Effects and Safety

Class Warnings

The typical class warnings are present in the lurasidone label (Sunovion Pharmaceuticals 2013), including the black box warning about increased stroke risk in elderly persons and a variety of other class warnings regarding neuroleptic malignant syndrome, tardive dyskinesia, diabetes, hyperlipidemia, weight gain, glucose abnormalities, hyperprolactinemia, agranulocytosis, suicide, and seizures. Lurasidone has no warning for QTc alteration; a dedicated cardiac safety study (referenced in the package insert) found no evidence of QTc prolongation with lurasidone treatment.

Adverse Event Reports

Safety information is available from the manufacturer's safety database (see also www.sunovionmedical.com/therapeutic_areas/psychiatry.html). Dose-related adverse effects that separated from placebo included somnolence, akathisia, and EPS (as measured by total scores on clinical rating scales for EPS). It is notable that weight and metabolic parameters were only minimally affected in patients with schizophrenia or bipolar depression in clinical trials. Although short-term changes in cholesterol, triglycerides, and glucose are likely to be attributable to the transition from medications with more substantial adverse profiles in these domains, the weight gain data for lurasidone are very noticeable and consistent.

Promising Features

Minimal Weight Gain

Lurasidone appears to have the promise of weight neutrality. Weight gain in pooled 6-week studies across doses was 0.75 kg; in the pooled 12-month database from extension studies, patients lost an average of 0.4 kg (Meyer *et al.* 2015). These statistics compare favorably with those for other antipsychotics in wide clinical use (see the review

by Citrome [2011b]). It is important to note that specific populations outside the current label may have a greater risk for weight gain compared with the typical patient with chronic schizophrenia in these trials. Data are not yet available for lurasidone's profile in the long-term treatment of bipolar depression. Nevertheless, the suggestion of no weight gain after a year's treatment, even for patients who may have gained weight with previous treatments, is quite promising.

Potential Cognitive Benefits

Basic Science Rationale

Compounds that interact with the 5-HT_7 receptor as their primary binding profile have historically been shown to produce beneficial cognitive effects in animal models (Ballaz *et al.* 2007). Furthermore, it is postulated that agents with partial agonist properties at the 5-HT_{1A} receptor may have potential benefit in regard to a reduction in flat affect and related negative symptoms in schizophrenia (Newman-Tancredi 2010).

Dizocilpine (MK-801) is a glutamate receptor antagonist that is used to induce cognitive impairments in healthy individuals that are quite similar to those seen in schizophrenia. Like other *N*-methyl-D-aspartate antagonists, MK-801 is capable of inducing deficits in memory and problem-solving. Given that *N*-methyl-D-aspartate antagonists such as ketamine and phencyclidine can induce a reliable analog of schizophrenia in healthy people (and exacerbate psychosis in patients with schizophrenia), such manipulations have more intrinsic validity than cholinergic manipulations, such as scopolamine challenge. In rats, lurasidone has shown the potential to reverse MK-801-induced learning and memory deficits in the passive avoidance test (Ishiyama *et al.* 2007) and the Morris water maze (Enomoto *et al.* 2008).

Research using analogs of cognitive impairment derived from animal models has notoriously failed to yield paradigms with adequate translational relevance to the specific cognitive domains affected in schizophrenia, particularly in terms of reliably predicting beneficial cognitive effects associated with pharmacological treatment (Harvey 2009). A possible reason for this failure may be that the adverse influences on human cognition of dopamine D_2 receptor antagonism associated with antipsychotic treatment may override the influences of a secondary receptor profile, preventing its beneficial effects from being realized (Harvey and McClure 2006). For example, ziprasidone, a partial agonist at the 5-HT_{1A} receptor, has never demonstrated greater cognitive benefit than antipsychotics that do not interact with that receptor (e.g., olanzapine [Harvey *et al.* 2004]). Thus, clear evidence of cognitive enhancement in patients with schizophrenia treated with the medication of interest, compared with other treatments in similar populations, is the bottom-line requirement for demonstration of meaningful cognitive benefit.

Studies in Schizophrenia and Bipolar Disorder

Three published studies in patients with schizophrenia have addressed the issue of lurasidone's cognitive benefit compared with that of other antipsychotics (Harvey *et al.* 2011, 2013, 2015), and a single study has examined cognitive benefits in bipolar disorder (Yatham *et al.* 2017).

The first study, which was conducted during the early development of lurasidone, was a 3-week double-blind, randomized head-to-head comparison of lurasidone and

ziprasidone in generally clinically stable outpatients with schizophrenia (Harvey *et al.* 2011). At the time this study was conducted, no U.S. patients had ever been exposed to lurasidone. Patients were selected for being naive to treatment with ziprasidone as well. The study examined changes in performance on a neuropsychological assessment consisting of most of the tests in the widely used Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Nuechterlein *et al.* 2008) and an interview-based assessment of cognitive functioning, the Schizophrenia Cognition Rating Scale (SCoRS; Keefe *et al.* 2006). The study found that lurasidone was associated with improvements on neuropsychological tests that were generally consistent with practice effects (Harvey *et al.* 2011). There was one exception, processing speed, which manifested relatively greater improvement with lurasidone than with ziprasidone. However, the improvements seen with lurasidone on the SCoRS were double the size of the improvements seen on the neuropsychological assessments and were nearly significantly larger than the improvements associated with ziprasidone. These results cannot be attributed to practice effects, given that the SCoRS is an interview, not a performance-based measure. Furthermore, the fact that the differential effects of lurasidone and ziprasidone were nearly significant ($P < 0.06$) argues against a generalized bias effect, because the lurasidone effects were clearly larger.

The second study (Harvey *et al.* 2013) compared two dosages of lurasidone (80 mg/day and 160 mg/day) with 600 mg/day quetiapine XR and placebo. This double-blind, placebo-controlled trial was conducted in patients experiencing an acute exacerbation of psychosis. Lurasidone 160 mg/day was compared with placebo, quetiapine XR, or lurasidone 80 mg/day over a 6-week period, followed by a 6-month double-blind extension. Follow-ups were conducted at 3 and 6 months, and patients receiving placebo were switched to lurasidone at flexible dosages; patients taking quetiapine XR continued to receive the same treatment. The CogState Computerized Cognitive Battery (Pietrzak *et al.* 2009) and the University of California San Diego Performance-based Skills Assessment--Brief version (Mausbach *et al.* 2007; Patterson *et al.* 2001) were administered at baseline and at each assessment point. When patients who provided invalid baseline CogState data were censored from the analysis, lurasidone 160 mg/day separated from placebo on composite cognitive improvement at the 6-week endpoint, whereas lurasidone 80 mg/day and quetiapine XR did not.

Harvey *et al.* (2015) presented an analysis of the dose-response relationships of lurasidone compared with quetiapine XR during the full 6-month duration of the trial. The full sample, regardless of the validity of baseline performance, was examined at two follow-up assessments (at 3 and 6 months). Lurasidone at both dosages (80 mg/day and 160 mg/day) was found to be superior to quetiapine XR at both assessments (Harvey *et al.* 2015). Scores on the University of California San Diego Performance-based Skills Assessment--Brief version improved with all active treatments at each of the assessment time points, with no between-group differences in improvements.

Although these results clearly require replication, they suggest that lurasidone may have beneficial cognitive effects. In all three studies, performance-and interview-based assessments of functionally relevant cognitive processes showed treatment-related improvements. In the Harvey *et al.* (2013) study, the performance-based cognitive assessments also showed improvements that were superior to those seen with placebo or the active comparator. This superiority to the comparator was confirmed across all dosages of lurasidone in the Harvey *et al.* (2015) study. The sleepiness-inducing effects of quetiapine XR may have contributed to the difference between this compound and lurasidone (Loebel *et al.* 2014c); however, this would not explain the separation of lurasidone from placebo.

The Yatham *et al.* (2017) study in bipolar disorder was an open-label augmentation study that added lurasidone 20-80 mg/day (mean dosage 48 mg/day) to treatment as usual in a randomized, open-label study design. Participants who took lurasidone improved by an effect size of $d = 0.48$ on a modified version of the MATRICS Consensus Cognitive Battery, whereas participants who received treatment as usual showed an improvement with retesting of $d = 0.04$ ($P < 0.03$). However, adverse event were reported by 60% of participants in the lurasidone group, which suggests that augmentation therapy may be challenging from a safety perspective.

Conclusion

Lurasidone is a newer antipsychotic with some benefits compared with other available medications, including a low propensity for weight gain and reduced risk for metabolic side effects. Little of the published data have been supported by sources other than the sponsor of the medication. We will watch this medication carefully to continue to determine its benefit over time. Since the previous edition of this textbook was published, the efficacy of lurasidone in children and adolescents has been demonstrated for both current indications, and additional cognitive and long-term safety data have become available. No new safety concerns have emerged, and no new data raising questions about the drug's efficacy have appeared. As of 2023, lurasidone is now available as a generic medication in the United States, although in other countries around the world, such as Japan and China, the drug has several years of patent life remaining.

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CHAPTER 34

Cariprazine

Leslie Citrome, M.D., M.P.H.

Cariprazine (Vraylar) was initially discovered by Gedeon Richter Ltd. as RGH-188 (Kiss *et al.* 2010) and was further developed by Forest Laboratories. It was approved by the FDA in 2015 for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults (U.S. Food and Drug Administration 2015) and by the European Medicines Agency in 2017 for the treatment of schizophrenia under the brand name Reagila (European Medicines Agency 2017). In 2019, cariprazine received approval by the FDA for the treatment of depressive episodes associated with bipolar I disorder in adults (bipolar depression; U.S. Food and Drug Administration 2019). In 2022, cariprazine received FDA approval for use as an adjunct to antidepressants for the treatment of major depressive disorder in adults (U.S. Food and Drug Administration 2022). Cariprazine is available in capsule strengths of 1.5, 3.0, 4.5, and 6.0 mg; however, not all doses are applicable for all indications (Allergan 2022).

Although cariprazine, a piperazine/piperidine derivative, is the third dopamine receptor partial agonist antipsychotic to become generally available, it differs from the other two, aripiprazole and brexpiprazole, in several respects (Citrome 2015). These differences include an almost 10-fold higher affinity for dopamine type 3 (D_3) versus type 2 (D_2) receptors (Table 34-1), which has potentially important clinical implications for the treatment of negative symptoms of schizophrenia and regulation of mood. In addition, when titrating the dosage of cariprazine, the extended half-life of its major active metabolite, didesmethyl-cariprazine (DDCAR) (Figure 34-1), needs to be considered (Citrome 2018).

TABLE 34-1. Pharmacodynamic profiles of cariprazine, aripiprazole, and brexpiprazole: in vitro binding affinities for human receptors

			Affinity K_i^a (in vitro)		
Receptor[b]		**Activity**	**Cariprazine**	**Aripiprazole**	**Brexpiprazole**
Dopamine	D_3	Partial agonist	0.085	0.8	1.1
	D_{2L}	Partial agonist	0.49	0.34	0.30
	D_{2S}	Partial agonist	0.69		
Serotonin	5-HT_{1A}	Partial agonist	2.6	1.7	0.12
	5-HT_{2A}	Antagonist	18.8	3.4	0.47
	5-HT_{2B}	Antagonist	0.58	0.36	1.9
	5-HT_{2C}	Antagonist	134	15	34
	5-HT_7	Antagonist	111	39	3.7
Histamine	H_1	Antagonist	23.2	61	19
Adrenergic	a_{1A}	Antagonist	155	57	3.8

		Affinity K_i^a (in vitro)		
Receptor[b]	**Activity**	**Cariprazine**	**Aripiprazole**	**Brexpiprazole**

[a] Receptor binding affinity K_i (nM), inverse relationship.

[b] Cariprazine and aripiprazole demonstrated negligible (percentage displacement < 20% at 1 mM test concentration) affinities for adrenergic (a_{2B}, a_{2C}), cannabinoid (CB_1, CB_2), dopamine (D_1, $D_{4.2}$, D_5), histamine (H_2, H_3, H_4), muscarinic (M_1, M_2, M_3, M_4, M_5), nicotinic, and serotonin (5-HT_3, 5-HT_4, 5-HT_{5A}, 5-HT_6) receptors (Kiss *et al.* 2010).

Source. Adapted from Table 2 (p. 1214) in Citrome L: "The ABC's of Dopamine Receptor Partial Agonists--Aripiprazole, Brexpiprazole and Cariprazine: The 15-Min Challenge to Sort These Agents Out." *International Journal of Clinical Practice* 69(11):1211-1220, 2015 (https://doi.org/10.1111/ijcp.12752). Copyright (c) 2015, John Wiley and Sons Ltd. Used with permission.

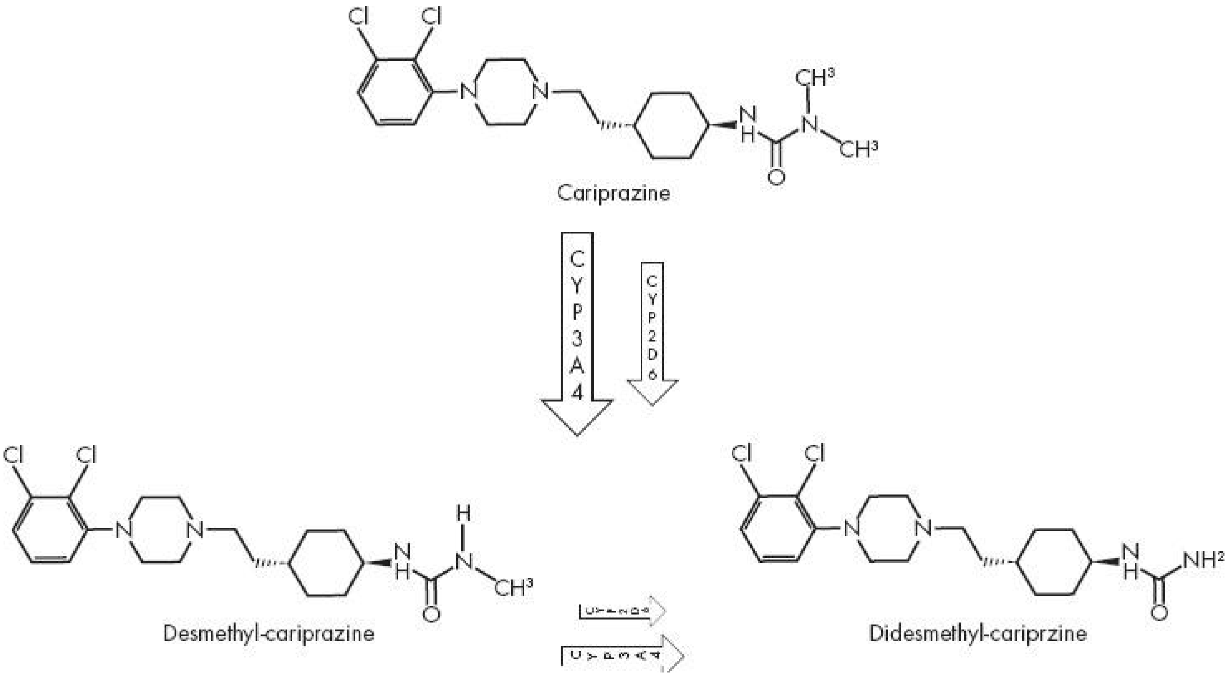


FIGURE 34-1. Chemical structures of cariprazine and its major metabolites, desmethyl-cariprazine and didesmethyl-cariprazine.

CYP = cytochrome P450.

Cariprazine is also being studied in adolescent patients (age 13-17 years) with schizophrenia (ClinicalTrials.gov identifier NCT03817502), in pediatric patients (age 10-17 years) with depressive episodes associated with bipolar I disorder (ClinicalTrials.gov identifier NCT04777357), and in pediatric patients (age 5-17 years) with irritability due to autism spectrum disorder (ClinicalTrials.gov identifier NCT05439616).

Pharmacodynamics

Structure

Cariprazine, also known as RGH-188 and MP-214, is 3-[4-{2-[4-(2,3-dichlorophenyl)piperazin-1-yl]ethyl}cyclohexyl]-1,1-dimethylurea (see Figure 34-1). The active ingredient is cariprazine hydrochloride, a compound synthesized and selected for development on the basis of its high selectivity for D_3 receptors over D_2 receptors (Kiss *et al.* 2010). Cariprazine has two clinically relevant active metabolites, desmethyl-cariprazine (DCAR) and DDCAR, whose pharmacology is like that of cariprazine (Kiss *et al.* 2019).

Receptor Binding Profile

Cariprazine is a potent D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors. This is a unique pharmacological profile among known antipsychotic medications (Kiss *et al.* 2010).

The theory behind the use of partial agonists, including cariprazine, is that these agents restore homeostatic balance to neurochemical circuits by 1) decreasing the effects of endogenous neurotransmitters (dopamine tone) in regions of the brain where their transmission is excessive, such as in the mesolimbic/striatal regions in schizophrenia or mania; 2) simultaneously increasing neurotransmission in regions where transmission of endogenous neurotransmitters is low, such as in the prefrontal cortex in schizophrenia; and 3) exerting little effect in regions where neurotransmitter activity is normal, such as in the pituitary gland.

Aripiprazole and brexpiprazole are also dopamine receptor partial agonists, with lower affinity for the dopamine D_3 receptor than for the D_2 receptor (Frankel and Schwartz 2017). In contrast, cariprazine has a six-to eightfold greater affinity for D_3 receptors than for D_2 receptors, with a specificity for D_3 receptors that is 3-10 times greater than aripiprazole's specificity for these receptors (Citrome 2015). There are other differences in the receptor-binding profiles of the three available dopamine receptor partial agonists, and these are outlined in Table 34-1. These profile differences can explain potential differences in tolerability among these choices. Moreover, the labeled indications for the three agents currently differ. In addition to its labeled indications for schizophrenia and for manic or mixed episodes associated with bipolar I disorder in adult or pediatric patients and as an adjunctive treatment for major depressive disorder in adults, aripiprazole is also approved for the treatment of irritability associated with autism spectrum disorder and for the treatment of Tourette's disorder in children (Otsuka 2022). Brexpiprazole is approved for use in treating schizophrenia in adults and in pediatric patients (ages 13 years and older), use as an adjunct to antidepressant treatment in major depressive disorder in adults, and also use as monotherapy for the treatment of agitation associated with dementia due to Alzheimer's disease (Otsuka 2023).

Cariprazine acts as a partial agonist at D_3 and D_2 receptors with very high binding affinity and at serotonin type 1A ($5\text{-}HT_{1A}$) receptors with high binding affinity (see Table 34-1). It acts as an antagonist at serotonin type 2B ($5\text{-}HT_{2B}$) and type 2A ($5\text{-}HT_{2A}$) receptors with very high and moderate binding affinity, respectively, and at histamine type 1 (H_1) receptors with moderate binding affinity. Cariprazine shows weak binding affinity for serotonin type 2C ($5\text{-}HT_{2C}$) and type 7 receptors, very low affinity for a_{1A}-adrenergic receptors, and no appreciable affinity for cholinergic muscarinic receptors (Allergan 2022; Kiss *et al.* 2010). Postsynaptic D_2 receptor antagonism/partial agonism in the striatum is thought to be the principal means by which currently available antipsychotic medications decrease the intensity and frequency of the positive symptoms of schizophrenia (McCutcheon *et al.* 2019).

D_3 Receptors

Dopamine, the neurotransmitter primarily linked to psychosis, has very high affinity for D_3 receptors. D_3 autoreceptors, which are primarily located in the limbic system, control phasic (not tonic) activity of dopamine nerve cells and mediate behavioral abnormalities induced by glutamatergic *N*-methyl-D-aspartate receptor antagonists (Kiss *et al.* 2021).

The signaling pathways of D_3 receptors are distinct from those of other dopamine receptors (Kiss *et al.* 2021). Selective D_3 receptor antagonism has therapeutic effects in schizophrenia and beyond, as demonstrated by improved cognitive function, emotion processing, executive function, flexibility, and social behavior in preclinical studies. D_3 receptor antagonism seems to contribute to the atypicality of antipsychotics by reducing motor extrapyramidal side effects (EPS); has no direct influence on prolactin release; and does not cause anhedonia, weight gain, or metabolic dysfunction (Gross and Drescher 2012; Gyertyan *et al.* 2011).

5-HT_{1A} Receptors

Cariprazine has a high affinity for human 5-HT_{1A} receptors and acts as a partial agonist at these receptors. The effect of cariprazine depends on the serotonin concentration at the site. Cariprazine's 5-HT_{1A} receptor partial agonism may contribute to its antidepressant efficacy (Blier and Ward 2003; El Mansari *et al.* 2020) and to its beneficial effects on negative symptoms and cognitive dysfunction in schizophrenia (Bantick *et al.* 2001; Sumiyoshi and Higuchi 2013), as suggested by preclinical studies.

5-HT_{2B} Receptors

Cariprazine has very high binding affinity for human 5-HT_{2B} receptors (K_i = 0.58 nM). Activity at these receptors may modulate dopamine release in the nucleus accumbens (Auclair *et al.* 2010; Devroye *et al.* 2017). Cariprazine's antagonist activity at 5-HT_{2B} receptors may contribute to its postulated effects on mood and cognition, as observed in preclinical studies.

5-HT_{2A} Receptors

Cariprazine's binding affinity for human 5-HT_{2A} receptors is lower than that of aripiprazole and brexpiprazole. In theory, antagonist effects at 5-HT_{2A} receptors are essential for the atypicality of antipsychotics (Mocci *et al.* 2014). It is unknown whether cariprazine's relatively low affinity for 5-HT_{2A} receptors has any clinical implications.

H_1 Receptors

Cariprazine's moderate affinity for H_1 receptors is roughly equivalent to the affinity of aripiprazole and brexpiprazole for these receptors (Citrome 2015). Sedation and orthostatic hypotension with high dosages of cariprazine might be related to this property; however, clinical trials have demonstrated a very low rate of sedation-or somnolence-related adverse events (Citrome 2018).

PET

In a Phase I open-label study, patients with schizophrenia received multiple-dosage cariprazine treatment for 15 days (Girgis *et al.* 2016). A clear dose-occupancy relationship existed for acute, day 4/5, and subchronic treatment, with the highest occupancy for both D_2 and D_3 receptors observed with the highest dosage (12 mg/day). For dosages of 12 mg/day, 3 mg/day, and 1 mg/day, respectively, the mean D_3 receptor occupancies were 99%, 92%, and 76%, and the mean D_2 receptor occupancies were 95%, 79%, and 45%. After subchronic (15-day) administration, cariprazine showed a threefold greater preference for D_3 versus D_2 receptors. The increased D_3/D_2 selectivity after subchronic dosing compared with acute dosing may be related to the pharmacological activity of cariprazine's metabolites.

Pharmacokinetics

In a Phase I double-blind, placebo-controlled tolerance study, the pharmacokinetic properties of cariprazine were similar in healthy volunteers and patients with schizophrenia (Kapas *et al.* 2008). Furthermore, a compartmental analysis revealed that changes in pharmacokinetic properties by age, sex, or race/ethnicity were not large enough to require dose adjustments (Periclou *et al.* 2021).

In premarketing studies investigating cariprazine's tolerability in specific populations, patients with either mild or moderate hepatic impairment (Child-Pugh score 5-9), in comparison with healthy subjects, had approximately 25% higher exposure (peak serum concentration and area under the curve) to the parent drug, and approximately 45% lower exposure to the major active metabolites (DCAR and DDCAR), following a single daily dose of 1 mg cariprazine or 0.5 mg cariprazine for 14 days. Pharmacokinetic analyses in patients with renal impairment showed no significant relationship between plasma clearance and creatinine clearance (Allergan 2022).

Absorption and Distribution

Cariprazine can be taken with or without food. Food causes a slight delay but has no significant effect on the extent of absorption (Meszaros *et al.* 2007).

The effect of a meal on the pharmacokinetics of cariprazine was evaluated in an open-label randomized crossover study in 12 healthy male volunteers who received a single oral dose of 2 mg. Time to maximum concentration (T_{max}) was observed at 3-4 hours under fasting conditions.

Previous consumption of a meal delayed absorption of the drug but did not affect the final extent of absorption. The plasma profile of cariprazine followed a multi-exponential disposition, with a terminal half-life of 5-6 days (Meszaros *et al.* 2007).

Peak serum concentrations are reached between 3 and 6 hours. There is a linear relationship between dose and plasma concentration. Cariprazine and its major active metabolites are highly bound (91%-97%) to plasma proteins (Allergan 2022). Cariprazine and DCAR reach steady-state concentrations within 1-2 weeks (Figure 34-2); by contrast, DDCAR requires 4-8 weeks of daily cariprazine administration to reach steady-state levels.

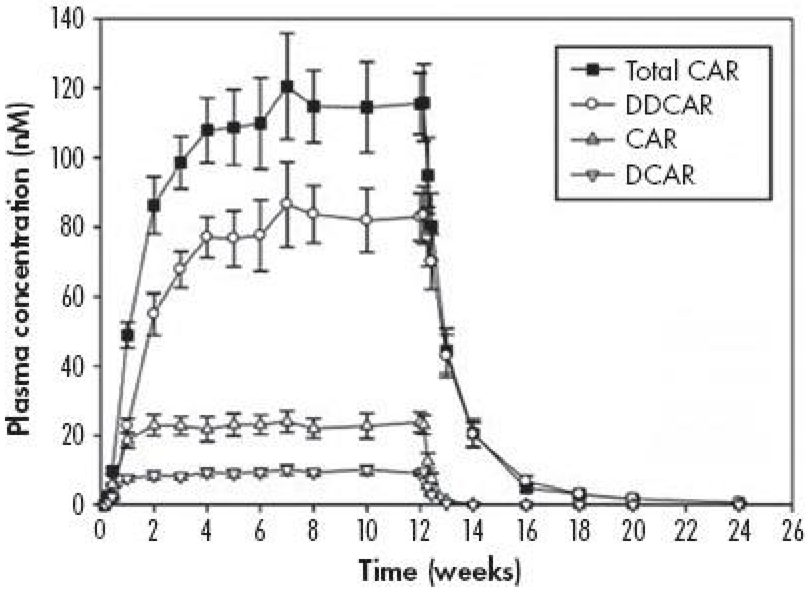


FIGURE 34-2. Plasma concentration at trough (mean +- SE) over time during and following 12 weeks of treatment with cariprazine 6 mg/day.

DDCAR is the predominant circulating moiety, representing about 70% of the total exposure. When treatment is discontinued, DDCAR concentrations persist longer than CAR or DCAR. CAR = cariprazine; DCAR = desmethyl-cariprazine; DDCAR = didesmethyl-cariprazine; total CAR = summed concentration of CAR, DCAR, and DDCAR.

Source. Adapted from Figure 1 (p. 30) in VRAYLAR(r) (cariprazine) full prescribing information. Revised 12/2022. Copyright (c) 2022 Allergan. All rights reserved. Available at: https://www.rxabbvie.com/pdf/vraylar_pi.pdf. Accessed July 7, 2023.

In a double-blind study of male patients with schizophrenia who were randomly assigned to cariprazine (0.5 mg/day increasing to 12.5 mg/day) or placebo, pharmacokinetic sampling was conducted for 37 days (Ereshefsky *et al.* 2008; Veselinovic *et al.* 2013). Systemic exposure to the metabolites DCAR and DDCAR was relatively low compared with exposure to the parent drug, cariprazine, on the first day of dosing (0.5 mg/day); however, on the last day of dosing (12.5 mg/day), systemic exposure to DDCAR was threefold greater than that to cariprazine for the plasma concentration area under the curve (AUC) over 24 hours and sixfold greater for the AUC over 7 days, indicating a slower elimination and a substantially longer half-life for DDCAR than for the parent compound. In a multicenter randomized, open-label, parallel-group 28-week study evaluating the pharmacokinetics of cariprazine and its two metabolites in 38 adult Japanese patients with schizophrenia, once-daily cariprazine at a fixed dosage (3, 6, or 9 mg/day) was administered. The effective half-life (calculated from time to steady state) of the total active moieties was approximately 1 week (Nakamura *et al.* 2016). Terminal half-lives of cariprazine, DCAR, and DDCAR ranged from 31.6 to 68.4 hours, 29.7 to 37.5 hours, and 314 to 446 hours, respectively.

According to a warning/precaution in cariprazine's product label, after cariprazine therapy is initiated or the dosage changed, response and side effects should be monitored for several weeks because of the long half-life of cariprazine's active metabolite DDCAR (Allergan 2022).

Metabolism and Elimination

Cariprazine is extensively metabolized by hydroxylation and demethylation in the liver cytochrome P450 (CYP) enzyme system, mainly by the 3A4 enzyme and to a lesser extent by the 2D6 enzyme. Eight metabolites for cariprazine were identified in liver microsomes (Kirschner *et al.* 2008), but only two active metabolites, DCAR and DDCAR, were clinically relevant (equipotent to cariprazine with similar receptor partial agonism [Kiss *et al.* 2019]; see also Figure 34-1).

Cariprazine's main metabolite, DCAR, is further metabolized by CYP3A4 and CYP2D6 to DDCAR, which is metabolized by CYP3A4 to a hydroxylated metabolite (Allergan 2022). In the Nakamura *et al.* (2016) study described above, cariprazine and DCAR levels had decreased by more than 90% 1 week after the last dose, whereas DDCAR levels had decreased by approximately 50% at 1 week; total active moieties had decreased by approximately 90% at 4 weeks. Cariprazine and its metabolites were eliminated almost completely in the 12 weeks following the last cariprazine dose (Nakamura *et al.* 2016).

Following administration of cariprazine 12.5 mg/day to patients with schizophrenia for 27 days, about 21% of the daily dose was found in urine, with approximately 1.2% of the daily dose excreted in urine as unchanged cariprazine (Allergan 2022).

Drug-Drug Interactions

Cariprazine and its major active metabolites are weak competitive inhibitors of the human CYP2D6 and CYP3A4 isozymes. They have no induction effect on the CYP enzyme system in human hepatocytes. Cariprazine is a weak inhibitor of several CYP isoenzymes in vitro: 1A2, 2C9, 2D6, 3A4, 2C19, 2A6, and 2E1 (Allergan 2022).

Because cariprazine is highly metabolized by CYP3A4 and metabolized to some degree by CYP2D6, changes in steady-state plasma concentrations would be expected if the drug were coadministered with potent CYP3A4 inhibitors or inducers. However, CYP2D6 inhibitors are not expected to significantly alter cariprazine metabolism, because CYP2D6 is known to be a relatively poor metabolizer of cariprazine and its metabolites, and CYP2D6 metabolizer status was not associated with any clinically relevant change in a population pharmacokinetic study (Periclou *et al.* 2021).

Taking a strong CYP3A4 inhibitor (e.g., ketoconazole) with cariprazine will increase concentrations of the parent drug by about 3.5-fold, decrease DCAR by about one-third, and increase DDCAR by about 1.5-fold. The concomitant use of CYP3A4 inducers with cariprazine has not yet been evaluated. When cariprazine is to be added to an existing regimen of a strong CYP3A4 inhibitor, the recommended starting dosage is 1.5 mg every other day, with a maximum dosage of 3 mg/day (Allergan 2022).

Indications, Dosing, and Efficacy

Cariprazine's half-life of more than 24 hours allows once-daily dosing, which is an advantage in terms of antipsychotic adherence. The cariprazine starting dosage is 1.5 mg/day for all indications. The recommended dosage is 1.5-6 mg/day for patients with schizophrenia, 3-6 mg/day for patients with bipolar mania, and 1.5 mg/day or 3 mg/day for patients with bipolar depression or for adjunctive use in major depressive disorder. Any dosage changes will be reflected fully in the serum level 2 weeks after initial dosing. In short-term controlled trials, dosages above 6 mg/day did not confer increased effectiveness sufficient to outweigh dosage-related adverse reactions (Allergan 2022).

FDA-Approved Indications

Acute Treatment of Schizophrenia

For the treatment of patients with schizophrenia, the recommended dosage of cariprazine is 1.5-6 mg/day. The recommended starting dosage of 1.5 mg/day can be increased to 3 mg/day on day 2, with further upward dosage increments of 1.5 mg/day or 3 mg/day as necessary, depending on clinical response and tolerability (Allergan 2022).

FDA approval for treating schizophrenia was based on data from three positive 6-week double-blind, randomized, placebo-controlled studies of cariprazine that were conducted in adult patients with schizophrenia between 2008 and 2011. Two of the studies used fixed dosages and included active drug controls (risperidone and aripiprazole) (Allergan 2022). All three trials consisted of a washout period of up to 1 week, 6 weeks of double-blind treatment, and a 2-week safety follow-up. The primary efficacy measure in each study was change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score; assessments were conducted at screening, at baseline, and at the end of each double-blind treatment week (weeks 1-6) (Table 34-2).

TABLE 34-2. Three 6-week randomized, placebo-controlled trials establishing the efficacy of cariprazine in treating acute schizophrenia

Trial[a]	Randomization (*N*)	Efficacy[b]	Side effects

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
NCT00694707	Total *N*: 732	At week 6, statistically significant LSMD in favor of cariprazine versus placebo were observed for	The most frequent cariprazine adverse events ([?] 5% and twice the rate of placebo) were akathisia, extrapyramidal disorder, insomnia, sedation, nausea, dizziness, and constipation.
RGH-MD-16	64% completed the study	* PANSS-Total (1.5 mg/day: [?] 7.6; 3 mg/day: [?] 8.8; 4.5 mg/day: [?] 10.4; $P < 0.001$ [LOCF]).	Mean changes in metabolic variables were small and similar between groups.
Phase II	Placebo (151)	* CGI-S (1.5 mg/day: [?] 0.4; 3 mg/day: [?] 0.5; 4.5 mg/day: [?] 0.6); $P < 0.001$ (LOCF) for 3 mg/day and 4.5 mg/day and $P < 0.01$ (LOCF) for 1.5 mg/day.	
(Durgam *et al.* 2014)	Cariprazine fixed	Risperidone was superior to	

Trial[a]	Randomization (N)	Efficacy[b]	Side effects
	dosages: 1.5 mg/day (145) 3 mg/day (147) 4.5 mg/day (148) Active control: Risperidone 4 mg/day (141)[c]	placebo on both measures (LSMD: PANSS = [?] 15.1; $P < 0.001$ [LOCF]; CGI-S = [?] 0.8; $P < 0.001$ [LOCF]).	
NCT01104766	Total N: 617	At week 6, statistically significant LSMD in favor of cariprazine versus placebo were observed for	Akathisia was reported ([?]5%; twice the rate of placebo).
RGH-MD-04	67% completed the study	* PANSS-Total (3 mg/day: [?] 6.0; $P = 0.0044$; 6 mg/day: [?] 8.8; $P < 0.0001$).	Changes in metabolic variables were small and similar to those with placebo.
Phase III	Placebo (153)	* CGI-S (3 mg/day: [?] 0.4; $P =$	

Trial[a]	Randomization (*N*)	Efficacy[b]	Side effects
		0.0044; 6 mg/day: [?] 0.5, $P <$ 0.0001).	
(Durgam *et al.* 2015a)	Cariprazine fixed dosages: 3 mg/day (155) 6 mg/day (157)	Aripiprazole was superior to placebo on both measures (LSMD: PANSS-Total = [?] 7.0; $P =$ 0.0008; CGI-S = [?] 0.4; $P =$ 0.0001). Active control: Aripiprazole 10 mg/day (152)[c]	
NCT01104779	Total *N*: 446	At week 6, statistically significant LSMD in favor of cariprazine versus placebo were observed for	The most frequent cariprazine adverse events ([?] 5%; twice the rate of placebo) in both cariprazine groups were akathisia, extrapyramidal disorder, and tremor; most were mild to moderate in severity.
RGH-MD-05	60.5% completed the	* PANSS-Total (3-6 mg/day:	Mean changes in metabolic variables

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
	study	[?] 6.8; $P = 0.003$; 6-9 mg/day: [?] 9.9; $P < 0.001$).	were generally small and similar between groups. Prolactin levels decreased in all groups.
Phase III	Placebo (147)	* CGI-S (3-6 mg/day: [?] 0.3; $P = 0.012$; 6-9 mg/day: [?] 0.5; $P < 0.001$).	
(Kane *et al.* 2015)	Cariprazine flexible dosing: 3-6 mg/day (151) 6-9 mg/day (148)		
	No active control group		

Note. CGI-S = Clinical Global Impression-Severity; LOCF = last observation carried forward; LSMD = least squares mean differences; PANSS = Positive and Negative Syndrome Scale.

[a] Trial registration: ClinicalTrials.gov identifiers NCT00694707, NCT01104766, and NCT01104779.

[b] In each study, the PANSS was used as the primary measure and the CGI-S rating scale was used as the secondary efficacy measure. The primary endpoint was change from baseline in PANSS total score at the end of week 6. The change from baseline for cariprazine and for all active control groups was superior to placebo in all three trials.

[c] The active control medications (aripiprazole and risperidone) were included for use in assessment of assay sensitivity and not for efficacy comparisons. However, they were superior to placebo.

As indicated in Table 34-2, patients were randomly assigned to receive cariprazine (1.5 mg/day, 3 mg/day, or 4.5 mg/day), risperidone (4 mg/day), or placebo in the NCT00694707 study; cariprazine (3 mg/day or 6 mg/day), aripiprazole (10 mg/day), or placebo in the NCT01104766 study; and cariprazine (3-6 mg/day or 6-9 mg/day) or placebo in the NCT01104779 study. The greater efficacy of cariprazine compared with placebo was demonstrated at dosages ranging from 1.5 mg/day to 9 mg/day. There was, however, a dosage-related increase in certain adverse effects (e.g., acute EPS), particularly at dosages above 6 mg/day (Kane *et al.* 2015). Findings regarding the time course of efficacy in the NCT01104766 study are shown in Figure 34-3 (Allergan 2022).

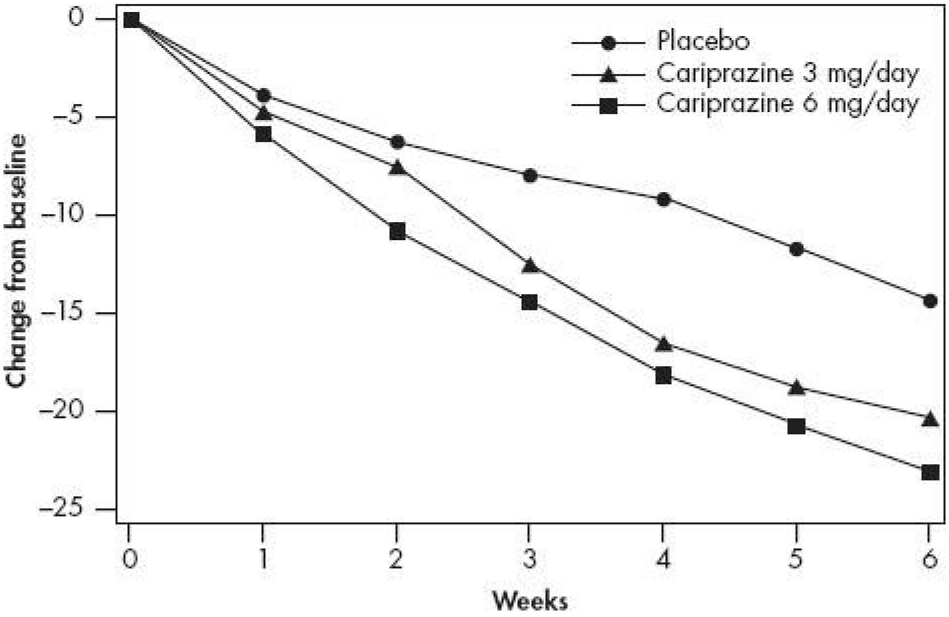


FIGURE 34-3. Change from baseline in Positive and Negative Syndrome Scale total score by weekly visit (ClinicalTrials.gov identifier: NCT01104766).

Source. Adapted from Figure 2 (p. 36) in VRAYLAR(r) (cariprazine) full prescribing information. Revised 12/2022. Copyright (c) 2022 Allergan. All rights reserved. Available at: https://www.rxabbvie.com/pdf/vraylar_pi.pdf. Accessed July 7, 2023.

In the Phase III clinical trials, dosages of 3-9 mg/day produced significant improvement on the PANSS and on the Clinical Global Impression Scale. Higher dosages (6-9 mg/day) showed early separation from placebo (by the end of week 1) but carried a dosage-related risk of adverse events (Kane *et al.* 2015), which led the FDA to recommend 6 mg/day as the maximum dosage (Citrome 2018).

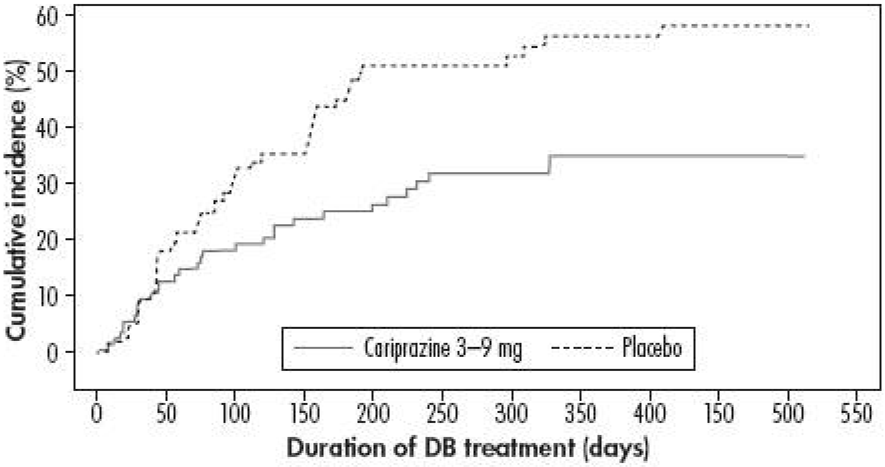
The effects of cariprazine on human cognition were evaluated in the NCT01104779 study (at weeks 0, 3, and 6). No significant differences were observed for the cariprazine group versus the placebo group on the

Cognitive Drug Research System Attention Battery Tests or the Color Trails Test (Kane *et al.* 2015).

An earlier Phase II 6-week double-blind, placebo-controlled proof-of-concept study (NCT00404573) evaluated the efficacy, safety, and tolerability of low-dosage (1.5-4.5 mg/day) versus high-dosage (6-12 mg/day) cariprazine in patients with schizophrenia. No significant differences between the two dosages of cariprazine and placebo were noted on PANSS total score changes or any other efficacy variables (Clinical Global Impression--Severity scale or PANSS subscales) after adjustment for multiplicity (Durgam *et al.* 2016d).

Maintenance Treatment of Schizophrenia

A supplemental new drug application for cariprazine for the maintenance treatment of adults with schizophrenia was approved by the FDA in November 2017 (U.S. Food and Drug Administration 2017) on the basis of a placebo-controlled, randomized withdrawal study in nonelderly adult patients with schizophrenia (Durgam *et al.* 2016b; Earley *et al.* 2018a). To participate in the trial, patients were required to be acutely ill at screening. During the 20-week open-label treatment phase, patients received cariprazine 3-9 mg/day (starting at 1.5 mg/day on day 1 and increasing to 3 mg/day on day 2); for patients with inadequate response and no significant tolerability issues, dosage increases were allowed on day 6 (6 mg/day [interim increase to 4.5 mg/day on day 4]) and day 10 (9 mg/day) if needed. Dosage decreases to 3 mg/day or 6 mg/day were allowed for patients with significant tolerability issues. To be eligible for random selection to either continue cariprazine or receive placebo, patients needed to meet prespecified stability criteria. Patients were required to be hospitalized during screening and for the first 2 weeks of the run-in phase. The double-blind, randomized phase consisted of 26-72 weeks of fixed-dose treatment at the same dosage as in the stabilization phase. The primary efficacy outcome was time to first relapse, defined by worsening of symptom scores, psychiatric hospitalization, aggressive/violent behavior, or risk for suicide. A total of 264 of 765 patients (34.5%) completed the open-label phase, and 200 patients were randomly assigned to a group. Demographic and baseline characteristics of the participants entering the open-label phase were like those for the acute short-term trials described earlier. The baseline PANSS score at the start of the double-blind phase was 51. About 50% of all cariprazine patients received 9 mg/day at randomization, 37% received 6 mg/day, and 14% received 3 mg/day. According to Kaplan-Meier analysis, time to relapse was significantly longer for patients who continued cariprazine than for patients randomly selected to receive placebo (hazard ratio 0.45, 95% CI 0.28-0.73). A sensitivity analysis conducted in response to an FDA request (Earley *et al.* 2018a) resulted in a hazard ratio of 0.52 (95% CI 0.33-0.82), as shown in the product label (Allergan 2022). Of note, between-group separation between cariprazine and placebo did not occur until around day 50 (Figure 34-4), possibly because of the long half-life of cariprazine (and specifically DDCAR) (Correll *et al.* 2019).



At Risk	Cariprazine 3–9 mg	101	81	72	64	54	48	44	38	32	26	18	0
	Placebo	99	75	58	54	38	32	28	23	23	21	16	0
Event	Cariprazine 3–9 mg	0	12	18	22	24	28	28	30	30	30	30	30
	Placebo	0	17	30	32	45	45	46	48	48	49	49	49

FIGURE 34-4. Kaplan-Meier curves of cumulative rate of relapse during double-blind (DB) treatment.

Although this study permitted dosing of cariprazine at 3-9 mg/day, the maximum recommended daily dosage was 6 mg. Between-group separation of the curves did not occur until around day 50, possibly because of the long half-life of cariprazine (and specifically didesmethyl-cariprazine [DDCAR]) lending some extended protection against the risk of relapse.

Source. Adapted from Figure 3 (p. 37) in VRAYLAR(r) (cariprazine) full prescribing information. Revised 12/2022. Copyright (c) 2022 Allergan. All rights reserved. Available at: https://www.rxabbvie.com/pdf/vraylar_pi.pdf. Accessed July 7, 2023.

Additional Study for Negative Symptoms in Schizophrenia

Cariprazine's European summary of product characteristics (European Medicines Agency 2023) includes support for its efficacy for treating predominantly negative symptoms in patients with schizophrenia based on a 26-week double-blind, randomized study that compared cariprazine 4.5 mg/day with risperidone 4 mg/day in 460 nonelderly adult patients (Nemeth *et al.* 2017). There was no placebo control. In this study, patients were required to have a PANSS negative factor score of at least 24, with single-item scores of at least 4 (moderate) on selected symptoms, such as blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation. Excluded were patients with a hospital admission or an acute exacerbation of schizophrenia within the 6 months prior to the study, a PANSS positive factor score greater than 19, significant fluctuations in positive or negative symptoms during the prospective lead-in period, treatment with clozapine in the 12 months prior to the study, moderate to severe depressive symptoms, clinically relevant parkinsonian symptoms, or treatment with antidepressant medications and/or anticholinergic medications (for abnormal movements). From randomization (day 0) to day 6, patients received cariprazine 1.5 mg/day or risperidone 2 mg/day. On days 7-13, patients received 3 mg/day of their respective study drug, and on day 14, patients received the target dosage of cariprazine 4.5 mg/day or risperidone 4 mg/day. Antipsychotic medication taken during the lead-in period was downtitrated during this period and discontinued on day 14. The dosage of the double-blind study medication could be decreased to 3 mg/day in the event of poor tolerability. In cases of impending psychotic deterioration, the dosage could be increased to 6 mg/day.

The subjects' mean age was 40 years, and 57% of patients were male. Overall, 77% of patients completed the double-blind treatment. The mean daily dosage was 4.2 mg for cariprazine and 3.8 mg for risperidone. Cariprazine was superior to risperidone on both the primary (PANSS negative factor score) and key secondary (Personal and Social Performance Scale) outcomes, with a modest effect size. For outcome variables analyzed to assess pseudospecific effects (change from baseline in PANSS positive symptoms, depression, and parkinsonian symptoms), changes were small and similar for cariprazine and risperidone. These results thus excluded indirect effects related to positive, depressive, or EPS improvement as a factor in improvement in negative symptoms. The most common adverse event for cariprazine was akathisia (8%), which was also observed in 5% of persons randomly selected to receive risperidone.

The study awaits replication. It has generated robust debate regarding the limitations of current approaches to the treatment of negative symptoms of schizophrenia (Kantrowitz 2021, 2022; Nemeth *et al.* 2022).

Acute Manic or Mixed Episodes Associated With Bipolar I Disorder

Cariprazine's efficacy in the treatment of bipolar manic or mixed episodes was established at dosages ranging from 3 mg/day to 12 mg/day. Dosages higher than 6 mg/day did not appear to add additional benefit over lower dosages, and there was a dosage-related increase in certain adverse effects (e.g., acute EPS). Therefore, the maximum recommended dosage is 6 mg/day. Findings on the time course of efficacy in the NCT01058668 study are shown in Figure 34-5 (Allergan 2022).

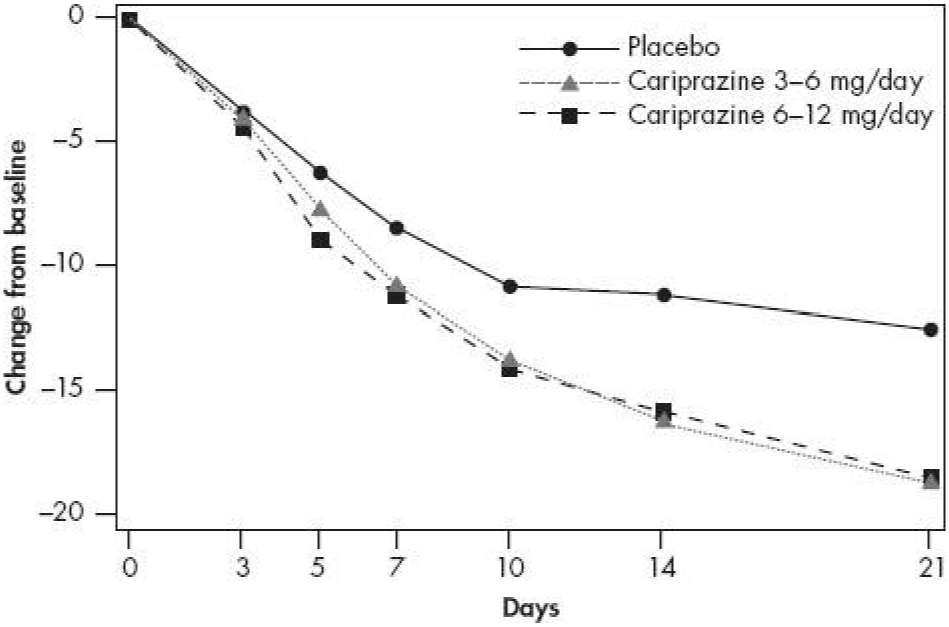


FIGURE 34-5. Change from baseline in Young Mania Rating Scale total score by study visit (ClinicalTrials.gov identifier: NCT01058668).

Source. Adapted from Figure 4 (p. 39) in VRAYLAR(r) (cariprazine) full prescribing information. Revised 12/2022. Copyright (c) 2022 Allergan. All rights reserved. Available at: https://www.rxabbvie.com/pdf/vraylar_pi.pdf. Accessed July 7, 2023.

FDA approval for the bipolar disorder indication was based on data from three 3-week placebo-controlled trials in adults with manic or mixed episodes of bipolar I disorder with or without psychotic features. All three studies demonstrated cariprazine's superiority over placebo (Table 34-3).

TABLE 34-3. Three 3-week randomized, placebo-controlled, flexibly dosed trials establishing the efficacy of cariprazine in acute manic/mixed episodes of bipolar I disorder

Trial[a]	Randomization (*N*)	Efficacy[b]	Side effects

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
NCT01058668	Total *N*: 497	At week 3, statistically significant LSMD in favor of cariprazine versus placebo were observed for	The most common ([?] 5%; twice the rate of placebo) treatment-related adverse events for cariprazine were akathisia (both groups) and nausea, constipation, and tremor (6-12 mg/day only).
Phase III	74% completed the study	* YMRS-Total (3-6 mg/day: [?] 6.1; 6-12 mg/day: [?] 5.9; *P* < 0.001 [both]).	There were no statistically significant differences between cariprazine and placebo in mean change from baseline in metabolic variables, liver enzymes, or prolactin, with the exception of increased triglycerides in the 3-6 mg/day group.
(Calabrese *et al.* 2015)	Cariprazine flexible dosing: 3-6 mg/day (167) 6-9 mg/day (169) Placebo (161)	* CGI-S (3-6 mg/day: [?] 0.6; 6-12 mg/day: [?] 0.6; *P* < 0.001 [both]).	

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
NCT00488618	Total *N*: 238	At week 3, statistically significant LSMD in favor of cariprazine versus placebo were observed for	The most common adverse events (> 10% for cariprazine) were extrapyramidal disorder, headache, akathisia, constipation, nausea, and dyspepsia.
Phase II	63% completed the study	* YMRS-Total (3-12 mg/day: [?] 6.1; $P < 0.001$).	Changes in metabolic variables were similar between groups, with the exception of fasting glucose change.
(Durgam *et al.* 2015b)	Cariprazine flexible dosing: 3-12 mg/day (118) Placebo (120)	* CGI-S (3-12 mg/day: [?] 0.6; $P < 0.001$).	
NCT01058096	Total *N*: 312	At week 3, statistically significant LSMD in favor of cariprazine versus placebo were observed for	The most common cariprazine-related (> 10%; twice the rate of placebo) treatment-emergent adverse events were akathisia, extrapyramidal disorder, tremor, dyspepsia, and vomiting.

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
Phase III	69% completed the study	* YMRS-Total (3-12 mg/day: [?] 4.3; *P* = 0.0004).	Mean changes from baseline in metabolic variables were generally small and similar between groups.
(Sachs *et al.* 2015)	Cariprazine flexible dosing: 3-12 mg/day (158) Placebo (154)	* CGI-S (3-12 mg/day: [?] 0.4; *P* = 0.0027).	

Note. CGI-S = Clinical Global Impression-Severity; LSMD = least squares mean differences; YMRS-Total = Young Mania Rating Scale total score.

[a] Trial registration: ClinicalTrials.gov identifiers NCT01058668, NCT00488618, and NCT01058096.

[b] In all trials, patients were adults (ages 18-65 years; mean age = 39 years) whose symptoms met DSM-IV-TR criteria for bipolar I disorder with manic or mixed episodes and with or without psychotic features (YMRS score [?] 20). YMRS and CGI-S were used as the primary and secondary efficacy measures, respectively; the primary endpoint was decrease from baseline in YMRS-Total score at the end of week 3. The change from baseline for cariprazine was superior to placebo in all three trials. All three trials lacked an active control arm and had a short duration.

Bipolar Depression

Cariprazine monotherapy received approval by the FDA in 2019 for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) (U.S. Food and Drug Administration 2019). The efficacy of cariprazine for this indication was established in one 8-week (Durgam *et al.* 2016c) and two 6-week (Earley *et al.* 2019, 2020a) fixed-dose placebo-controlled trials in patients (mean age 41.6 years, range 18-65 years) whose symptoms met DSM-IV-TR (American Psychiatric Association 2000) or DSM-5 (American Psychiatric Association 2013) criteria for depressive episodes associated with bipolar I disorder (Table 34-4). In each study, the primary endpoint was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at the end of week 6

(Allergan 2022). In each study, the cariprazine 1.5 mg/day dosage demonstrated statistical significance over placebo, but the same was not true for cariprazine 3 mg/day (Citrome 2019). Findings on the time course of efficacy in the NCT02670551 study are shown in Figure 34-6 (Allergan 2022). An earlier study that had tested flexible dosing of cariprazine in two ranges (0.25-0.75 mg/day and 1.5-3 mg/day) failed to demonstrate statistical separation from placebo (Yatham *et al.* 2020).

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TABLE 34-4. One 8-week and two 6-week randomized, placebo-controlled, fixed-dose trials establishing the efficacy of cariprazine in treating depressive episodes associated with bipolar I disorder (bipolar depression)

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
NCT01396447	Total *N*: 584	Study was conducted over 8 weeks. At week 6,	The most common ([?] 5%; twice the rate of placebo)

Note. CGI-S = Clinical Global Impression--Severity; LSMD = least squares mean differences using a mixed-effects model for repeated measures; MADRS-Total = Montgomery-Asberg Depression Rating Scale total score.

[a] Trial registration: ClinicalTrials.gov identifiers NCT01396447, NCT02670551, and NCT02670538.

[b] In all trials, patients were adults (ages 18-65 years; mean age 42 years) whose symptoms met DSM-IV-TR (American Psychiatric Association 2000) or DSM-5 (American Psychiatric Association 2013) criteria for depressive episodes associated with bipolar I disorder. MADRS and CGI-S were used as the primary and secondary efficacy measures, respectively; the primary endpoint was decrease from baseline in the MADRS-Total score at the end of week 6. The change from baseline for cariprazine was superior to that for placebo in all three trials for the 1.5 mg/day dosage. All three trials lacked an active control arm and were of short duration.

Trial[a]	Randomization (*N*)	Efficacy[b]	Side effects
		statistically significant LSMD in favor of cariprazine vs. placebo were observed for	treatment-related adverse event for cariprazine was akathisia (3 mg/day).
Phase II	73% completed the study	* MADRS-Total (1.5 mg/day: [?] 4.0; *P* = 0.003); result was not statistically significant for cariprazine 0.75 mg/day or 3 mg/day vs. placebo.	Rates of weight gain were generally low and descriptively similar for placebo and cariprazine.
(Durgam *et al.* 2016c)	Cariprazine fixed dosages:	* CGI-S (1.5 mg/day: [?] 0.4; *P* = 0.013); result was not statistically significant for cariprazine 0.75	

Note. CGI-S = Clinical Global Impression--Severity; LSMD = least squares mean differences using a mixed-effects model for repeated measures; MADRS-Total = Montgomery-Asberg Depression Rating Scale total score.

[a] Trial registration: ClinicalTrials.gov identifiers NCT01396447, NCT02670551, and NCT02670538.

[b] In all trials, patients were adults (ages 18-65 years; mean age 42 years) whose symptoms met DSM-IV-TR (American Psychiatric Association 2000) or DSM-5 (American Psychiatric Association 2013) criteria for depressive episodes associated with bipolar I disorder. MADRS and CGI-S were used as the primary and secondary efficacy measures, respectively; the primary endpoint was decrease from baseline in the MADRS-Total score at the end of week 6. The change from baseline for cariprazine was superior to that for placebo in all three trials for the 1.5 mg/day dosage. All three trials lacked an active control arm and were of short duration.

Trial[a]	Randomization (*N*)	Efficacy[b]	Side effects
		mg/day or 3 mg/day vs. placebo.	
	0.75 mg/day (143) 1.5 mg/day (147) 3 mg/day (146) Placebo (148)		
NCT02670551	Total *N*: 488	At week 6, statistically significant LSMD in favor of cariprazine vs. placebo were observed for	The most common ([?] 5%; twice the rate of placebo) treatment-related adverse events for cariprazine were nausea (3 mg/day), dizziness (1.5 mg/day), sedation (1.5 mg/day), and akathisia (1.5 mg/day).

Note. CGI-S = Clinical Global Impression--Severity; LSMD = least squares mean differences using a mixed-effects model for repeated measures; MADRS-Total = Montgomery-Asberg Depression Rating Scale total score.

[a] Trial registration: ClinicalTrials.gov identifiers NCT01396447, NCT02670551, and NCT02670538.

[b] In all trials, patients were adults (ages 18-65 years; mean age 42 years) whose symptoms met DSM-IV-TR (American Psychiatric Association 2000) or DSM-5 (American Psychiatric Association 2013) criteria for depressive episodes associated with bipolar I disorder. MADRS and CGI-S were used as the primary and secondary efficacy measures, respectively; the primary endpoint was decrease from baseline in the MADRS-Total score at the end of week 6. The change from baseline for cariprazine was superior to that for placebo in all three trials for the 1.5 mg/day dosage. All three trials lacked an active control arm and were of short duration.

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
		* MADRS-Total (1.5 mg/day: [?] 2.5; 3 mg/day, [?] 3.0; *P* = 0.0331 and 0.0103, respectively). * CGI-S; result was not statistically significant for cariprazine 1.5 mg/day or 3 mg/day vs. placebo.	Cariprazine at both dosages resulted in non-clinically significant metabolic changes and weight gain.
Phase III (Earley *et al.* 2019)	Cariprazine fixed dosages: 1.5 mg/day (160) 3 mg/day (165) Placebo (163)		

Note. CGI-S = Clinical Global Impression--Severity; LSMD = least squares mean differences using a mixed-effects model for repeated measures; MADRS-Total = Montgomery-Asberg Depression Rating Scale total score.

[a] Trial registration: ClinicalTrials.gov identifiers NCT01396447, NCT02670551, and NCT02670538.

[b] In all trials, patients were adults (ages 18-65 years; mean age 42 years) whose symptoms met DSM-IV-TR (American Psychiatric Association 2000) or DSM-5 (American Psychiatric Association 2013) criteria for depressive episodes associated with bipolar I disorder. MADRS and CGI-S were used as the primary and secondary efficacy measures, respectively; the primary endpoint was decrease from baseline in the MADRS-Total score at the end of week 6. The change from baseline for cariprazine was superior to that for placebo in all three trials for the 1.5 mg/day dosage. All three trials lacked an active control arm and were of short duration.

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
	84% completed the study		
NCT02670538	Total *N*: 493	At week 6, statistically significant LSMD in favor of cariprazine vs. placebo were observed for	The most common ([?] 5%; twice the rate of placebo) treatment-related adverse events for cariprazine were nausea (1.5 mg/day), fatigue (1.5 mg/day), and akathisia and restlessness (3 mg/day).
Phase III	81% completed the study	* MADRS-Total (1.5 mg/day: [?] 2.5; $P = 0.0417$); result was not statistically significant for cariprazine 3	Cariprazine at both dosages resulted in low rates of weight gain.

Note. CGI-S = Clinical Global Impression--Severity; LSMD = least squares mean differences using a mixed-effects model for repeated measures; MADRS-Total = Montgomery-Asberg Depression Rating Scale total score.

[a] Trial registration: ClinicalTrials.gov identifiers NCT01396447, NCT02670551, and NCT02670538.

[b] In all trials, patients were adults (ages 18-65 years; mean age 42 years) whose symptoms met DSM-IV-TR (American Psychiatric Association 2000) or DSM-5 (American Psychiatric Association 2013) criteria for depressive episodes associated with bipolar I disorder. MADRS and CGI-S were used as the primary and secondary efficacy measures, respectively; the primary endpoint was decrease from baseline in the MADRS-Total score at the end of week 6. The change from baseline for cariprazine was superior to that for placebo in all three trials for the 1.5 mg/day dosage. All three trials lacked an active control arm and were of short duration.

Trial[a]	Randomization (*N*)	Efficacy[b]	Side effects
		mg/day vs. placebo.	
(Earley *et al.* 2020a)	Cariprazine fixed dosages: 1.5 mg/day (168) 3 mg/day (158) Placebo (167)	* CGI-S (1.5 mg/day: [?] 0.3; *P* = 0.0417); result was not statistically significant for cariprazine 3 mg/day compared with placebo.	

Note. CGI-S = Clinical Global Impression--Severity; LSMD = least squares mean differences using a mixed-effects model for repeated measures; MADRS-Total = Montgomery-Asberg Depression Rating Scale total score.

[a] Trial registration: ClinicalTrials.gov identifiers NCT01396447, NCT02670551, and NCT02670538.

[b] In all trials, patients were adults (ages 18-65 years; mean age 42 years) whose symptoms met DSM-IV-TR (American Psychiatric Association 2000) or DSM-5 (American Psychiatric Association 2013) criteria for depressive episodes associated with bipolar I disorder. MADRS and CGI-S were used as the primary and secondary efficacy measures, respectively; the primary endpoint was decrease from baseline in the MADRS-Total score at the end of week 6. The change from baseline for cariprazine was superior to that for placebo in all three trials for the 1.5 mg/day dosage. All three trials lacked an active control arm and were of short duration.

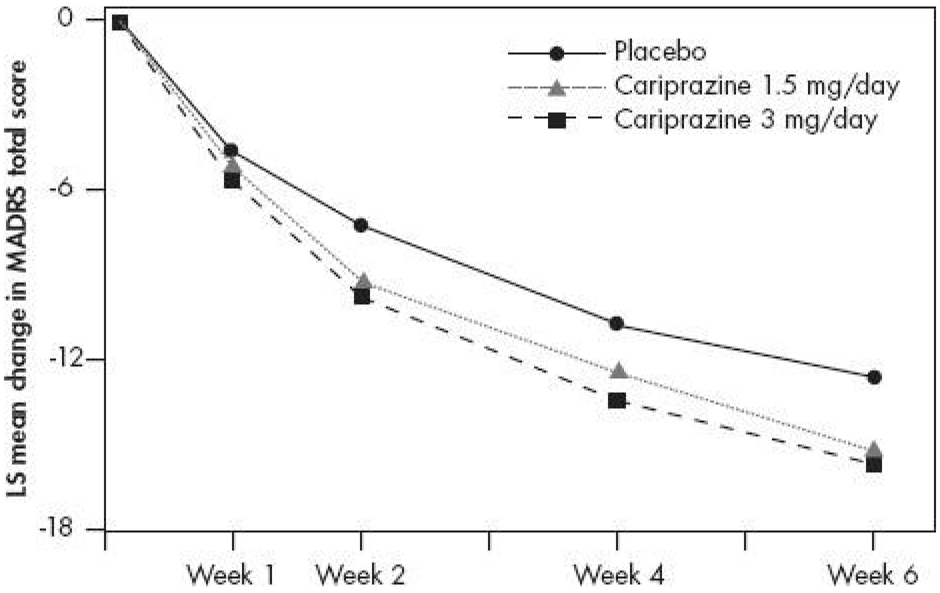

FIGURE 34-6. Least squares (LS) mean change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score by study visit (ClinicalTrials.gov identifier: NCT02670551).

Source. Adapted from Figure 5 (p. 41) in VRAYLAR(r) (cariprazine) full prescribing information. Revised 12/2022. Copyright (c) 2022 Allergan. All rights reserved. Available at: https://www.rxabbvie.com/pdf/vraylar_pi.pdf. Accessed July 7, 2023.

Adjunctive Use in Major Depressive Disorder

Cariprazine received FDA approval in 2022 for use as adjunctive therapy to antidepressants in the treatment of major depressive disorder in adults (U.S. Food and Drug Administration 2022). The efficacy of cariprazine for this indication was established in an 8-week (Durgam *et al.* 2016a) and a 6-week (Sachs *et al.* 2023) placebo-controlled trial in patients (mean age 45 years, range 18-65 years) whose symptoms met DSM-IV-TR (American Psychiatric Association 2000) or DSM-5 (American Psychiatric Association 2013) criteria for major depressive disorder (with or without symptoms of anxiety) and who had experienced an inadequate response to 1 to 3 courses of prior antidepressant therapy. Inadequate response during antidepressant treatment was defined as less than 50% improvement to antidepressant treatment of adequate dosage and duration (Table 34-5). In each study, the primary endpoint was change from baseline in the MADRS total score at study endpoint (Allergan 2022). Statistically significant differences versus placebo for 2-4.5 mg/day but not 1-2 mg/day was found in one study (Durgam *et al.* 2016a), and statistically significant differences from placebo for adjunctive cariprazine 1.5 mg/day but not 3 mg/day was found in the other (Sachs *et al.* 2023). No statistically significant differences versus placebo were found for adjunctive cariprazine 0.1-0.3 mg/day or 1-2 mg/day in another study (Fava *et al.* 2018), and no statistically significant differences for cariprazine 1.5-4.5 mg/day versus placebo were observed in a fourth published study (Earley *et al.* 2018b). Lastly, an additional Phase III study was completed that did not demonstrate statistically significant differences from placebo for either 1.5 mg/day or 3 mg/day (Riesenberg *et al.* 2023). Findings on the time course of efficacy in the NCT03738215 study (Sachs *et al.* 2023) are shown in Figure 34-7 (Allergan 2022).

TABLE 34-5. One 8-week and one 6-week randomized, placebo-controlled trial establishing the efficacy of adjunctive cariprazine in treating major depressive disorder

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
NCT01469377	Total *N*: 819	At week 8, statistically significant LSMD in favor of cariprazine vs. placebo were observed for	The most common ([?] 5%; twice the rate of placebo) treatment-related adverse events for cariprazine was akathisia (both groups), insomnia (2-4.5 mg/day), nausea (2-4.5 mg/day), restlessness (both groups), somnolence (2-4.5 mg/day), fatigue (2-4.5 mg/day), tremor (2-4.5 mg/day), dizziness (2-4.5

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
			mg/day), constipation (2-4.5 mg/day), and increased appetite (2-4.5 mg/day.
Phase II	82% completed the study	* MADRS-Total (2-4.5 mg/day: [?] 2.2; $P = 0.0114$); result was not statistically significant for cariprazine 1-2 mg/day vs. placebo.	Rates of weight gain were generally low and descriptively similar for placebo and cariprazine.
(Durgam *et al.* 2016a)	Cariprazine flexible dosing: 1-2 mg/day (274) 2-4.5 mg/day (276) Placebo (269)		
NCT03738215	Total N: 759	At week 6, statistically significant LSMD in favor of cariprazine vs. placebo were observed for	The most common ([?] 5%; twice the rate of placebo) treatment-related adverse events for cariprazine were akathisia (both groups) and nausea (both groups).

Trial[a]	**Randomization (*N*)**	**Efficacy**[b]	**Side effects**
Phase III	89% completed the study	* MADRS-Total (1.5 mg/day: [?] 2.5; *P* = 0.0025); result was not statistically significant for cariprazine 3 mg/day vs. placebo.	Cariprazine at both dosages resulted in non-clinically significant metabolic changes and weight gain.
(Sachs *et al.* 2023)	Cariprazine flexible dosing: 1.5 mg/day (252) 3 mg/day (253) Placebo (254)		

Note. LSMD = least squares mean differences using a mixed-effects model for repeated measures; MADRS-Total = Montgomery-Asberg Depression Rating Scale total.

[a] Trial registration: ClinicalTrials.gov identifiers NCT01469377 and NCT02670538.

[b] In all trials, patients were adults (ages 18-65 years; mean age 45 years) whose symptoms met DSM-IV-TR (American Psychiatric Association 2000) or DSM-5 (American Psychiatric Association 2013) criteria for major depressive disorder, with or without symptoms of anxiety and who had an inadequate response to 1 to 3 courses of prior antidepressant therapy. Inadequate response during antidepressant treatment was defined as less than 50% improvement to antidepressant treatment of adequate dosage and duration. MADRS was used as the primary efficacy measure; the primary endpoint was decrease from baseline in the MADRS-Total score at the end of week 8 (NCT01469377) or week 6 (NCT03738215). Both trials lacked an active control arm and were of short duration.

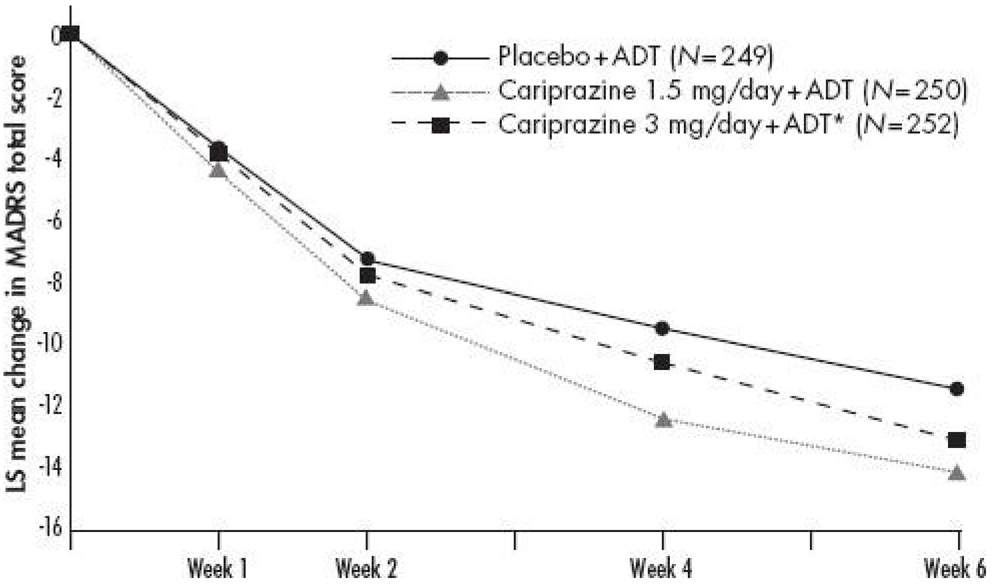

FIGURE 34-7. Least squares (LS) mean change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score by study visit (ClinicalTrials.gov identifier: NCT03738215).

ADT = antidepressant.

* Dosage was not clinically significant.

Source. Adapted from Figure 6 (p. 43) in VRAYLAR(r) (cariprazine) full prescribing information. Revised 12/2022. Copyright (c) 2022 Allergan. All rights reserved. Available at: https://www.rxabbvie.com/pdf/vraylar_pi.pdf. Accessed July 7, 2023.

In a pooled analysis of data from all five acute randomized, placebo-controlled clinical trials of adjunctive cariprazine in adults with major depressive disorder, cariprazine at dosages greater than or equal to 1 mg/day evidenced a statistically significant benefit on the categorical outcome of response (as measured by a 50% or greater decrease from baseline on the MADRS total score), with a dose-response relationship favoring better tolerability for the lower dosage range (1-2 mg/day or 1.5 mg/day) (Citrome et al 2023). Also supporting the indication for major depressive disorder was a Phase III multicenter long-term (26-week), flexible-dosage (1.5-4.5 mg/day) open-label safety study (Vieta *et al.* 2019) in which the mean change from the open-label baseline in the MADRS total score at week 26 was -7.3. By week 26, 53.3% of patients were in remission (defined as a MADRS total score [?] 10).

Side Effects and Toxicology

Cariprazine was generally well tolerated in the short-term trials for schizophrenia, bipolar I mania, bipolar I depression, and adjunctive use in major depressive disorder. No significant anticholinergic or antiadrenergic treatment-emergent adverse events (TEAEs) were documented, because cariprazine has negligible affinity for cholinergic and adrenergic receptors (Allergan 2022).

Atypical Antipsychotic Class Warnings

Numerous risks are associated with the use of atypical antipsychotic medications in general. As a member of this class, and because of its antidepressant indication, cariprazine carries the following warnings and precautions (Allergan 2022):

1. Increased mortality in elderly patients with dementia-related psychosis
2. Suicidal thoughts and behaviors in children, adolescents, and young adults
3. Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis
4. Neuroleptic malignant syndrome
5. Tardive dyskinesia
6. Metabolic changes
7. Leukopenia, neutropenia, and agranulocytosis
8. Orthostatic hypotension and syncope
9. Falls
10. Seizures

11. Potential for cognitive and motor impairment
12. Body temperature dysregulation
13. Dysphagia

These warnings are based on the pharmacological actions of this class (Citrome and Nasrallah 2012). In the front section of the product label containing "Highlights of Prescribing Information," the most common adverse reactions--defined as an incidence of at least 5% and at least twice the rate of placebo--are listed by approved indication (Allergan 2022). For schizophrenia, the most common adverse reactions are EPS and akathisia; for bipolar mania, EPS, akathisia, dyspepsia, vomiting, somnolence, and restlessness; for bipolar depression, nausea, akathisia, restlessness, and EPS; and for adjunctive treatment of major depressive disorder, akathisia, restlessness, fatigue, constipation, nausea, insomnia, increased appetite, dizziness, and EPS. Differences in rates of some adverse events (e.g., akathisia) have emerged because of study design variations in details including dosage, titration, and study duration.

Late-Occurring Adverse Drug Reactions

Cariprazine has a long half-life, but the half-life of its major metabolite, DDCAR, is even longer. Therefore, plasma levels accumulate over time, and side effects may appear weeks after the initiation of treatment. As a result, the incidence of adverse reactions in short-term trials may not reflect the rates after longer-term exposure. Clinicians are advised to monitor for adverse reactions for several weeks after a patient begins taking cariprazine and after any dosage increase. If side effects are noted, dosage reduction or medication discontinuation should be considered (Allergan 2022).

Akathisia and Acute Extrapyramidal Symptoms

In a post hoc analysis that evaluated the safety and tolerability of cariprazine in the acute treatment of schizophrenia, data from four 6-week randomized, double-blind, placebo-controlled trials of cariprazine were used to examine modal daily dosage subgroups of cariprazine 1.5-3 mg/day, 4.5-6 mg/day, and 9-12 mg/day (Earley *et al.* 2017a). A dose-response relationship was observed for akathisia and EPS. Most events of akathisia and EPS were considered mild or moderate in severity. Rates of discontinuation for EPS, akathisia, and restlessness were less than or equal to 2% among cariprazine-treated patients. During double-blind treatment, the mean duration of akathisia was 24 days for cariprazine-treated patients and 29 days for placebo-treated patients. The onset of akathisia generally occurred within 2-3 weeks of the initiation of cariprazine treatment.

In a post hoc analysis that evaluated the safety and tolerability of cariprazine in the treatment of bipolar mania, data were taken from three 3-week randomized, double-blind, placebo-controlled, flexible-dosage trials of cariprazine 3-12 mg/day (Earley *et al.* 2017b). The incidence of treatment-emergent akathisia and parkinsonism was higher in both cariprazine groups (3-6 mg/day and 9-12 mg/day) than in the placebo group. Most incidents of EPS-related TEAEs in both cariprazine groups were considered to be mild or moderate, and EPS-related TEAEs rarely led to study discontinuation. Akathisia and EPS onset peaked approximately 2 weeks after the start of treatment for both placebo-and cariprazine-treated patients; the mean duration of akathisia was 15 days and 14 days in the placebo and cariprazine groups, respectively. When examined by modal daily dosage, the data revealed a dose-response relationship for cariprazine for the TEAE of EPS.

A post hoc analysis was done for patients with bipolar depression and focused specifically on akathisia, restlessness, and EPS (Citrome *et al.* 2021). Among participants

in the three fixed-dosage, 6-or 8-week clinical studies of cariprazine 1.5 mg/day and 3 mg/day in bipolar depression, the incidence of akathisia was 7.6% for cariprazine overall (1.5 mg/day, 5.5%; 3 mg/day, 9.6%) and 2.1% for placebo; acute EPS occurred in 4.5% of cariprazine-treated patients (1.5 mg/day, 3.8%; 3 mg/day, 5.1%) and 2.1% of placebo-treated patients. Most TEAEs were mild/moderate, occurred during the first 3 weeks of cariprazine initiation or dose increase, and resulted in few discontinuations (< 3%); median time to resolution of an akathisia or EPS TEAE after the last dose of cariprazine was approximately 1 week. Rescue medication was used by fewer than 3% of patients to manage akathisia/EPS events. Citrome and colleagues concluded that cariprazine-related akathisia and EPS can be minimized with conservative dosing and titration strategies.

Changes in Metabolic and/or Clinical Laboratory Variables

In the previously described pooled post hoc analysis of tolerability of cariprazine in the acute treatment of schizophrenia (Earley *et al.* 2017a) over 6 weeks, cariprazine-treated patients showed a decrease in mean total cholesterol, fasting low-density lipoprotein cholesterol, and triglyceride levels, whereas placebo-treated patients showed increases from baseline in these variables. The decrease in high-density lipoprotein cholesterol was similar for cariprazine and placebo, as was the increase in mean fasting blood glucose. Clinically relevant shifts in lipid and glucose variables were similar for cariprazine and placebo. The percentage of patients with an increase in fasting glucose of 10 mg/dL or greater was higher in the cariprazine group than in the placebo group; however, no clear dose-response relationship was observed. A weight increase of at least 7% was observed in 9.2% of cariprazine-treated patients and 4.7% of placebo-treated patients. Both mean weight change and shifts in weight of at least 7% were larger in the 9-12 mg/day dosage group, a dosage range that is not approved for use. Within the recommended cariprazine dosage range (1.5-6 mg/day), mean weight gain was 0.8-1.0 kg for cariprazine; the proportions of patients with a weight increase of at least 7% were 7.6% and 7.7% for the 1.5-3 mg/day and the 4.5-6 mg/day groups, respectively. There was no increase in prolactin level or in the incidence of electrocardiogram QTc interval greater than 500 milliseconds.

In the previously mentioned pooled post hoc analysis of tolerability of cariprazine in the acute treatment of bipolar mania (Earley *et al.* 2017b), changes in metabolic variables were small and were generally similar between cariprazine and placebo groups; mean increases in fasting glucose levels were greater with cariprazine (3-6 mg/day, 6.6 mg/dL; 9-12 mg/day, 7.2 mg/dL) than with placebo (1.7 mg/dL). Mean weight changes were 0.54 kg and 0.17 kg for cariprazine and placebo, respectively; fewer than 3% of all patients experienced a weight increase of at least 7%. Mean prolactin levels decreased in all treatment groups. Cariprazine was not associated with clinically meaningful changes in electrocardiographic variables; three patients had a corrected QT interval by Bazett (QTcB) greater than 500 milliseconds (two in the placebo group and one in the cariprazine 9-12 mg/day group).

In a pooled post hoc analysis of tolerability of cariprazine in the acute treatment of bipolar depression (Earley *et al.* 2020b), mean weight gain was less than 1 kg for cariprazine-treated patients; a body weight increase of at least 7% was observed in fewer than 4% of patients in each cariprazine modal dosage group. Metabolic changes were small and were generally similar for cariprazine and placebo; mean increase in glucose

was 3.1 mg/dL for cariprazine and 2.6 mg/dL for placebo. Fixed-dosage and modal dosage findings were generally consistent; values for most metabolic variables were slightly higher for a fixed dosage of 3 mg/day than 1.5 mg/day. Regarding prolactin levels, cariprazine-treated patients had a slight mean increase, and placebo-treated patients had a slight decrease. Mean changes in electrocardiographic variables were small and were similar for cariprazine and placebo; one patient in the cariprazine 1.5 mg/day modal dosage group had a corrected QT interval by Fredericia (QTcF) greater than 500 milliseconds.

Longer-Term Open-Label Clinical Trials

12-Week Open-Label Study in Schizophrenia

In a 12-week open-label, fixed-dosage (3 mg/day, 6 mg/day, or 9 mg/day) study of 38 adult patients with schizophrenia (Nakamura *et al.* 2016) conducted in Japan, the overall completion rate was 63.2%; 15.8% of patients discontinued the medication because of adverse events. No abnormal laboratory values or major differences from baseline in EPS were observed. A total of 37 (97.4%) patients reported at least one TEAE, and 31 (81.6%) patients experienced at least one adverse drug reaction (defined as an adverse event for which a causal relationship with cariprazine was determined to be "reasonably possible" [Nakamura *et al.* 2016, p. 334]). Side effects observed in this study were similar to those reported in previous studies. Across all dosage groups, akathisia was observed in 21% of patients during cariprazine treatment. One case of cataract (deemed mild in severity) was reported.

20-Week Open-Label Treatment Phase From the Schizophrenia Maintenance Study

The most commonly observed adverse events during the open-label phase of the schizophrenia maintenance study (Durgam *et al.* 2016b; Earley *et al.* 2018a) were akathisia (19%), insomnia (14%), and headache (12%). Akathisia and other EPS adverse events (excluding akathisia or restlessness) each led to discontinuation in approximately 1% of patients in the open-label treatment phase, whereas no EPS-related adverse events led to discontinuation during double-blind treatment. Weight gain of at least 7% was reported in 11% of open-label patients and in 32% of placebo-treated patients and 27% of cariprazine-treated patients during double-blind treatment. Changes from baseline in lipid variables at the end of open-label and double-blind treatment were generally not clinically relevant. There were no clinically relevant mean changes in blood pressure, and no patients had an electrocardiogram QTc interval greater than 500 milliseconds.

48-Week Open-Label Studies in Schizophrenia

A report that pooled data from two 48-week studies ($N = 679$) of open-label, flexible-dosage cariprazine in adult patients with schizophrenia (NCT01104792, 3-9 mg/day; NCT00839852, 1.5-4.5 mg/day) reported an overall completion rate of 40.1% (Nasrallah *et al.* 2017). The overall mean daily dosage of cariprazine was 5.42 mg. The mean duration of treatment with cariprazine (days +- SD) was 188.4 +- 136.8. The individual study reports for each of these 48-week studies have also been published (Cutler *et al.* 2018; Durgam *et al.* 2017).

The incidence of TEAEs was 81.7% (Nasrallah *et al.* 2017). TEAEs reported in at least 10% of patients were akathisia (15.5%), insomnia (13.3%), headache (12.8%), and weight increase (10.5%) (Table 34-6). Serious adverse events were reported in 82 patients (12.1%) during the open-label treatment period, including one death (suicide). The most common serious adverse events were worsening of schizophrenia (4.4%) and psychotic disorder (2.1%).

TABLE 34-6. Most frequent[a] treatment-emergent adverse events (TEAEs) during long-term (48-week) treatment with cariprazine ($N = 679$)

TEAE	*n* (%)
Akathisia	105 (15.5)
Insomnia	90 (13.3)
Headache	87 (12.8)
Weight increase	71 (10.5)
Anxiety	58 (8.5)
Tremor	47 (6.9)
Extrapyramidal disorder	45 (6.6)
Schizophrenia	39 (5.7)
Nausea	38 (5.6)
Restlessness	38 (5.6)
Dyspepsia	37 (5.4)
Nasopharyngitis	34 (5.0)

[a] Reported by [?] 5% of patients.

Source. Adapted from Nasrallah *et al.* 2017. Copyright (c) 2017, The Authors. Open Access: Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

The mean increase in body weight was 1.58 kg (Table 34-7). A potentially clinically significant increase in body weight was seen in 27% of patients; a potentially clinically significant decrease was seen in 11% of patients. Mean changes from baseline to the end of the study in metabolic variables and other clinical laboratory values, blood pressure, and electrocardiographic variables were generally small. The mean increase in fasting glucose (4.5 mg/dL) was similar to that observed during the 6-week lead-in studies. Mean alanine transaminase and aspartate transaminase values increased slightly. Creatine kinase levels increased slightly during open-label treatment; however, a large standard deviation indicates that the data were highly variable. No patients' symptoms met criteria for Hy's law (regarding risk of fatal drug-induced liver injury). Mean prolactin levels decreased from baseline to the end of the study. The incidence of treatment-emergent parkinsonism (measured by the Simpson-Angus Scale) was 10.7%, and the incidence of treatment-emergent akathisia (measured by the Barnes Akathisia Rating Scale) was 17.8%. Ophthalmological testing revealed no significant ocular changes. There was no mean increase in the QTc interval. A greater-than-60-millisecond increase in the QTcB value occurred in 7 patients (1.0%) overall, whereas a greater-than-60-millisecond increase in the QTcF value occurred in 2 patients (0.3%) overall. Three patients (0.4%) had a postbaseline QTcB value greater than 500 milliseconds; one of these patients (0.2%) also had a postbaseline QTcF value greater than 500 milliseconds.

TABLE 34-7. Mean changes in metabolic and clinical laboratory variables after long-term treatment with cariprazine (*N* = 679)

Variables	**Mean change (*SD*)**

Note. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Source. Adapted from Nasrallah *et al.* 2017. Copyright (c) 2017, The Authors. Open Access: Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Variables	**Mean change (*SD*)**
Metabolic laboratory variables	
Total cholesterol, mg/dL	[?] 5.3 (31.1)
LDL cholesterol, mg/dL	[?] 3.5 (26.4)
HDL cholesterol, mg/dL	[?] 0.8 (11.3)
Triglycerides, mg/dL	1.2 (87.2)
Fasting glucose, mg/dL	4.5 (23.2)
Body weight	
Body weight, kg	1.58 (5.42)
Potentially clinically significant changes (7%) in body weight, %	
[?] 7% increase from baseline: 27.2	
[?] 7% decrease from baseline: 10.9	
Prolactin	
Prolactin, ng/mL	[?] 15.4 (39.6)
Creatine kinase	
Creatine phosphokinase, U/L	18.5 (264.0)
Liver function	
Alanine aminotransferase, U/L	2.4 (27.8)
Aspartate aminotransferase, U/L	0.5 (15.5)
Total bilirubin, mg/dL	0.02 (0.28)

Note. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Source. Adapted from Nasrallah *et al.* 2017. Copyright (c) 2017, The Authors. Open Access: Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

16-Week Open-Label Study in Bipolar Mania

In a 16-week study ($N = 402$) of open-label, flexible-dosage cariprazine (3-12 mg/day) in adult patients with bipolar mania (Ketter *et al.* 2018), the overall completion rate was 33%; 16% of patients discontinued the medication because of adverse events. The mean treatment duration was 57.7 days, and the mean cariprazine dosage was 6.2 mg/day. No deaths were reported.

The incidence of TEAEs was 83.3% (Ketter *et al.* 2018). TEAEs reported in at least 10% of patients were akathisia (32.6%), headache (16.7%), constipation (10.7%), and nausea (10.4%). On the basis of EPS rating scales, treatment-emergent parkinsonism and akathisia were observed in 8.7% of patients and 36.8% of patients, respectively. Although 37.6% patients had TEAEs of akathisia/restlessness, only 4.7% of patients discontinued cariprazine because of akathisia. Of new cases of akathisia/restlessness, 94% were reported during the first 4 weeks of treatment; only nine new cases were reported from week 5 to week 16. Most TEAEs of akathisia/restlessness (98%) were considered mild or moderate in severity and related to treatment. The mean body weight increase was less than 1 kg; 9.3% of patients had a [?] 7% gain in body weight, and a [?] 7% loss in body weight was reported in 3.5% of patients. Mean changes in laboratory values, vital signs, electrocardiographic results, and ophthalmological variables were generally small. Cariprazine treatment was not associated with an increase in prolactin levels.

26-Week Open-Label Study in Major Depressive Disorder

In a Phase III open-label, long-term (26-week), flexible-dosage (1.5-4.5 mg/day) multicenter study of cariprazine used adjunctively with antidepressant therapy in adult patients, the completion rates were 66% for patients who had completed a lead-in study ($n = 311$) and 36% for patients who had been newly recruited ($n = 131$) (Vieta *et al.* 2019). A total of 79.4% of patients experienced a TEAE, with 97.1% of these considered mild or moderate. The most common TEAEs were akathisia (15.9%) and headache (11.6%). Mean changes in clinical laboratory, cardiovascular, and ophthalmological variables were generally not clinically relevant. The most common TEAEs leading to discontinuation were akathisia (2.9%), restlessness (2.0%), anxiety (1.7%), and fatigue (1.2%). Two deaths occurred (one traffic accident and one completed suicide), both of which were considered unrelated to treatment.

High Dosage and Overdose

In premarketing clinical trials involving cariprazine in approximately 5,000 patients or healthy subjects, accidental acute overdosage (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered the same day (Allergan 2022).

Use During Pregnancy and Lactation

There have been no well-controlled studies of cariprazine in pregnant women, but neonates whose mothers have been exposed to other antipsychotic medications during the third trimester of pregnancy are at risk for EPS and withdrawal symptoms following delivery (Allergan 2022).

Administration of cariprazine to rats during the period of organogenesis caused malformations, lower pup survival, and developmental delays at drug exposures less than the human exposure at the maximum recommended human dosage of 6 mg/day. However, cariprazine was not teratogenic in rabbits at doses up to 4.6 times the maximum recommended human dosage of 6 mg/day. Thus, some animal data suggest that cariprazine may cause fetal harm. Pregnant women should be advised of the potential risk to the fetus (Allergan 2022).

Conclusion

Cariprazine combines functional selectivity at D_3 and D_2 receptors, partial agonist activity at 5-HT_{1A} receptors, and antagonism at 5-HT_{2B} and, to a lesser extent, 5-HT_{2A} receptors. Cariprazine's receptor binding profile is unique, with the highest affinity and selectivity for D_3 receptors of any second-generation antipsychotic. The long half-life of its predominant circulating active metabolite, DDCAR, permits every-other-day dosing when lower dosages are required. Cariprazine is approved as a monotherapy for use in treating schizophrenia, bipolar I mania, and bipolar I depression and as an adjunctive therapy for major depressive disorder. Adverse reactions (incidence [?] 5% and at least twice the rate of placebo) listed in the product label and common to all four indications are EPS and akathisia. Cariprazine is relatively well tolerated in terms of weight gain, metabolic variables, and sedation/somnolence, and it has no deleterious effect on prolactin or the electrocardiogram QT interval.

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CHAPTER 35

Pimavanserin

Jeffrey Cummings, M.D., Sc.D.(HS)

Pimavanserin (Nuplazid) occupies a unique niche in the neuropsychopharmacological armamentarium. It was the first agent approved to treat any neuropsychiatric syndrome in any neurodegenerative disease. It is currently one of only two such agents (brexpiprazole is approved to treat agitation in Alzheimer's disease). Pimavanserin is approved by the FDA to treat hallucinations and delusions in Parkinson's disease. Given the high prevalence of neuropsychiatric symptoms in neurodegenerative disorders, it is remarkable that only one agent has been approved to treat this key aspect of these common conditions (Cummings 2021). Details of the drug's history, structure-activity relations, pharmacological profile, pharmacokinetics, indications and efficacy, side effects and toxicology, and drug-drug interactions are presented in this chapter.

Pimavanserin is currently available as a 10-mg tablet and a 34-mg capsule, and no generic equivalent products are marketed at present. The capsule may be swallowed whole or opened and sprinkled on certain soft foods for ease of administration (Acadia Pharmaceuticals 2023).

History and Discovery

Pimavanserin was discovered as the result of a rational discovery program. It was noted that the common feature of most atypical antipsychotics was that they were highly potent serotonin type 2A (5-HT$_{2A}$) receptor inverse agonists or antagonists and were less potent dopamine type 2 receptor antagonists. This finding led to the hypothesis that highly selective 5-HT$_{2A}$ receptor inverse agonists/antagonists might have antipsychotic properties with more desirable side-effect profiles compared with agents with concomitant dopamine receptor blockade. A functional receptor selection and amplification assay for 5-HT$_{2A}$ receptor inverse agonists using overexpression of 5-HT$_{2A}$ receptors in the embryonic mouse fibroblast cell line NIH/3T3 with a marker gene to permit signal detection with a colorimetric method was developed for high-throughput screening (Hacksell *et al.* 2014). Thirteen thousand small molecules were assessed; of 500 initial hits, 100 were shown to be 5-HT$_{2A}$ inverse agonists. One of these agents had the desired receptor engagement profile, with nearly 100-fold selectivity for 5-HT$_{2A}$ receptors over serotonin type 2B, serotonin type 2C (5-HT$_{2C}$), and serotonin type 6 receptors. The initial hit compound had poor oral availability. A lead optimization campaign was initiated to develop an orally available analogue; ACP-103 (pimavanserin/Nuplazid) was the product of the lead optimization enterprise (Hacksell *et al.* 2014).

Structure-Activity Relations

Pimavanserin tartrate salt has the chemical name urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N* -[[4-(2-methylpropoxy)phenyl]methyl]-, (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1) (Cruz 2017). The molecular formula of pimavanserin free base is $(C_{25}H_{34}FN_3O_2)_2$. The molecular weight of pimavanserin free base is 427.55 (Cruz 2017).

The 5-HT$_{2A}$ receptor is a G protein-coupled receptor that interacts with the G proteins and other transducing molecules (Sullivan *et al.* 2015). 5-HT$_{2A}$ inverse agonists block metabotropic glutamate receptors 2/3 and increase release of dopamine in mesolimbic and mesocortical brain regions (Sullivan *et al.* 2015; Wischhof and Koch 2016). The 5-HT$_{2A}$ receptor is widely distributed in the brain and is most abundant in the neocortex (Lopez-Gimenez and Gonzalez-Maeso 2018). This same receptor has been implicated in mediating the psychotogenic effects of hallucinogens such as lysergic acid diethylamide (LSD) that are 5-HT$_{2A}$ receptor agonists (Gonzalez-Maeso *et al.* 2008). The structure of pimavanserin and its position when docked in the 5-HT$_{2A}$ receptor are shown in Figure 35-1.

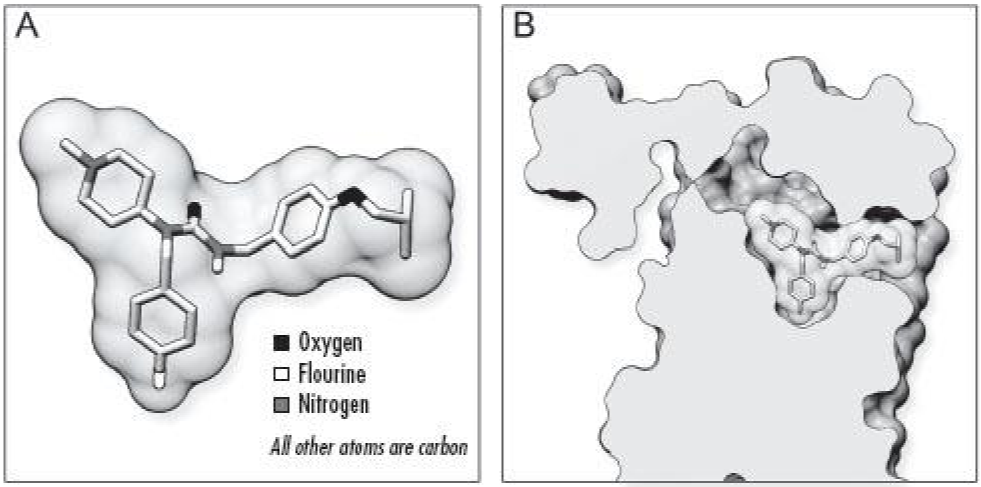

FIGURE 35-1. (A) Structure of pimavanserin and (B) pimavanserin docked in the binding pocket of the serotonin type 2A receptor.

Source. Model constructed with UCSF Chimera (Resource for Biocomputing, Visualization, and Informatics, University of California, San Francisco) and AutoDock Vina. Copyright (c) J. Cummings; illustrator, Mike de la Flor, Ph.D.

Structure-activity relations for a receptor and its companion transmitter must be seen in the circuit context in which the receptor occurs. Human cognition and behavior are emergent properties of circuits, and the treatment effect at the circuit level is critical to the efficacy of a transmitter-based intervention (Krakauer *et al.* 2017; Mill *et al.* 2017). The circuit impact of a treatment for psychosis that occurs with different types of neurodegenerative disorders may result from a final common pathway for psychosis involving dysregulation of cortical and limbic pathways, including serotonergic, GABAergic, glutamatergic, and dopaminergic signaling. The imbalance in cortical and mesolimbic excitatory tone involves circuits with 5-HT_{2A} receptors across types of neurodegenerative disease, providing an opportunity for modulation of psychotic symptoms in multiple disorders with a 5-HT_{2A} inverse agonist/antagonist (Cummings *et al.* 2022). The 5-HT_{2A} receptor is well represented in the amygdala, a structure involved in emotional behavior and included in the circuits affected by many neurodegenerative disorders and plausibly involved in psychosis with neurodegenerative disorders (Bombardi 2014). Genetic studies have found correlations between specific polymorphisms of the 5-HT_{2A} receptor gene and the presence of psychotic and other behavioral symptoms in Alzheimer's disease (Holmes *et al.* 1998, 2007; Lam *et al.* 2004). These polymorphisms in the 5-HT_{2A} receptor may contribute to the variable occurrence of psychosis in patients with neurodegenerative disorders.

Pharmacological Profile

Pimavanserin exhibits inverse agonist/antagonist activity at the 5-HT_{2A} receptor and to a lesser extent at the 5-HT_{2C} receptor. Pimavanserin has a 100-fold lower affinity for 5-HT_{2C} than 5-HT_{2A} (Caraci *et al.* 2020; Hacksell *et al.* 2014). Unlike most other atypical antipsychotics, it lacks significant antagonism of adrenergic, dopaminergic, histaminergic, and muscarinic receptors (Yunusa *et al.* 2020).

Pimavanserin activity has been assessed in animal models used to interrogate possible antipsychotic profiles of an agent. In one study, pimavanserin attenuated head-twitch behavior and prepulse inhibition deficits induced in rats by a 5-HT_{2A} receptor agonist and reduced hyperactivity induced in mice by an *N*-methyl-D-aspartate receptor noncompetitive antagonist, thereby demonstrating effects consistent with a 5-HT$_{2A}$ receptor mechanism of action in vivo and antipsychotic-like efficacy (Vanover *et al.* 2006).

In an animal model relevant to Parkinson's disease and to psychosis, animals with bilateral 6-hydroxydopamine lesions of the substantia nigra displayed motoric impairments characteristic of humans with Parkinson's disease and exhibited augmented head twitches, increased amphetamine-induced locomotor activity, and disrupted prepulse inhibition, behavioral indices frequently used to assess antipsychotic activity in animal models. Pimavanserin reversed the psychosis-like behavioral deficits without exacerbating the motor deficits. The selective 5-HT$_{2A}$ inverse agonist M100907, but not the selective 5-HT$_{2C}$ inverse agonist SB 242084, paralleled the effects of pimavanserin, supporting the conclusion that the effects were mediated through 5-HT$_{2A}$ receptors (McFarland *et al.* 2011).

Animal studies relevant to the treatment of psychosis in neurodegenerative disorders have been pursued. Mice that received an intracerebroventricular infusion of the amyloid b$_{(25-35)}$ peptide fragment showed Alzheimer's disease-like histopathology and a psychosis-related behavioral phenotype with enhanced responses to the psychostimulants 2,5-dimethoxy-4-iodoamphetamine hydrochloride and amphetamine as well as disrupted prepulse inhibition (Price *et al.* 2012). Treatment with pimavanserin prevented 2,5-dimethoxy-4-iodoamphetamine hydrochloride-induced head twitches, reversed the augmented locomotor response to amphetamine, and normalized prepulse inhibition. These observations suggest that amyloid-b pathology may induce alterations in serotonergic function that underlie a psychosis-like phenotype and that can be normalized by pimavanserin. Pimavanserin has also been reported to reduce amyloid-b protein and improve cognition in transgenic models of Alzheimer's disease in which this protein is overproduced (Yuede *et al.* 2021).

Pharmacokinetics

Pimavanserin was well tolerated in Phase I and Phase II studies; 100 mg qd was identified as the maximum tolerated dosage. Pimavanserin exhibits dose-proportional plasma exposure over a wide range of doses, and no food effects on bioavailability have been found (Hacksell *et al.* 2014). A PET study using the 5-HT$_{2A}$ radioligand 3-*N*-[^{11}C]-methylspiperone (^{11}C-NMSP) demonstrated that a 10-mg dose nearly completely occupied the visualized frontal lobe 5-HT$_{2A}$ receptors, and a 20-mg oral dose produced maximal binding in healthy volunteers (Nordstrom *et al.* 2008).

The half-life of pimavanserin is relatively long at 55-60 hours. Pimavanserin is detectable in the serum within 1 hour of oral administration, and the time to maximal serum concentration for a single 34-mg dose (the standard dose used in clinical studies) is 6-8 hours (Cruz 2017; Nordstrom *et al.* 2008; Yunusa *et al.* 2020). Pimavanserin is highly bound to plasma protein (approximately 95%).

Pimavanserin is metabolized primarily in the liver by the cytochrome P450 (CYP) enzymes 3A4 and 3A5 and to a lesser extent by CYP2J2, CYP2D6, and other CYP and flavin-containing monooxygenase enzymes. It neither inhibits nor induces CYP3A4 activity. Maximal plasma concentrations are increased 1.5-fold by strong CYP3A4 inhibitors such as ketoconazole. There is a single dominant metabolite--*N*-desmethylated pimavanserin (AC-279)--that has a half-life of 200 hours (Cruz 2017; Yunusa *et al.* 2020). Approximately 1% of the parent compound is excreted unchanged in the urine and feces (Cruz 2017). The pharmacokinetics of pimavanserin are not known to be affected by age, sex, ethnicity, or weight; the number of patients in ethnic minority groups included in trials is small. Doses of pimavanserin need not be adjusted in patients with mild to moderate renal impairment; use of pimavanserin is not recommended in those with severe renal impairment or hepatic compromise (Cruz 2017).

Indications and Efficacy

Hallucinations and Delusions in Parkinson's Disease Psychosis

Pimavanserin is approved by the FDA for the treatment of hallucinations and delusions associated with Parkinson's disease with and without dementia. The efficacy of pimavanserin for the treatment of impulse-control disorders in Parkinson's disease, depression in Parkinson's disease, and insomnia in PTSD is being explored in clinical trials (see ClinicalTrials.gov).

Pimavanserin was assessed as an adjunctive to antidepressant treatment for major depressive disorder and was found not to have benefit in this setting. In a Phase II trial of pimavanserin for the treatment of negative symptoms in patients with schizophrenia, the active treatment group showed significantly greater improvement compared with the placebo group on the primary outcome, the Negative Symptom Assessment-16 (Business Wire 2019).

With its approval in 2016 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP), pimavanserin became the first psychotropic agent approved to treat any neuropsychiatric syndrome in any neurodegenerative disease. Brexpiprazole has since been approved for treatment of agitation associated with dementia due to Alzheimer's disease. The receptor profile of pimavanserin--5-HT_{2A} inverse agonism/antagonism and an absence of antagonism for dopamine receptors--suggested that it would have a useful role in the treatment of PDP. Traditional dopamine-blocking antipsychotics exaggerate parkinsonism (Graham *et al.* 1998). Nonclinical studies showed that pimavanserin ameliorated psychosis-like behaviors in rodent models with parkinsonism (McFarland *et al.* 2011).

A 28-day randomized, placebo-controlled Phase II study of pimavanserin for PDP showed no difference between drug and placebo on the Scale for the Assessment of Positive Symptoms (SAPS) total score. Pimavanserin-treated patients had significantly greater improvement on the SAPS measures of hallucinations and delusions compared with those taking placebo. The Unified Parkinson's Disease Rating Scale domains of delusions and hallucinations were significantly more improved in patients receiving pimavanserin compared with those receiving placebo. Administration of pimavanserin was not associated with worsening of motor function, sedation, or hypotension (Meltzer *et al.* 2010).

Many items on the SAPS are symptoms that are common in schizophrenia but rare in Parkinson's disease. To advance a scale more appropriate for use in PDP trials, Voss *et al.* (2013) developed the shortened Scale for Assessment of Positive Symptoms for Parkinson's Disease (SAPS-PD). This tool was used in a pivotal trial of pimavanserin for PDP.

This pivotal trial of pimavanserin for the treatment of PDP was a 6-week randomized, double-blind, parallel-group, placebo-controlled trial of pimavanserin (40 mg/day [Cummings *et al.* 2014]). All eligible participants entered a 2-week lead-in period with psychosocial therapy to identify patients responsive to nonpharmacological treatment. Following the lead-in period, 199 participants were randomly assigned to active treatment or placebo. After 6 weeks of treatment, the pimavanserin-treated group had a significantly greater decrease in SAPS-PD score ([?] 5.79 points) compared with the placebo group ([?] 2.73 points). Secondary outcomes, including scores on the Clinical Global Impression--Severity (CGI-S) and Clinical Global Impression--Improvement (CGI-I) scales as well as on measures of caregiver burden, improved significantly in the active treatment group. Scores on measures completed by central trial raters, site raters, and caregivers provided convergent validity of the antipsychotic effects. Sleep was notably improved in those receiving pimavanserin (Cummings *et al.* 2014; Kitten *et al.* 2018). There was no worsening of motor function in the active treatment group. There were more dropouts in the pimavanserin group, in part because of hallucinations or delusions that occurred within 10 days of patients starting the study drug.

An exploratory outcome of the PDP trial was the assessment of nighttime sleep quality and daytime wakefulness with the Scales for Outcomes in Parkinson's Disease--Sleep and Scales for Outcomes in Parkinson's Disease--Daytime Sleepiness (SCOPA-DS) (Marinus *et al.*

2003). Significantly greater improvement in both nighttime sleep quality and daytime sleepiness was observed in the group receiving pimavanserin compared with the group receiving placebo (Cummings *et al.* 2014). Pooled data from two trials provided additional evidence showing a sleep benefit in patients being treated for PDP with pimavanserin (Patel *et al.* 2018). Polysomnographic studies in healthy adult volunteers receiving pimavanserin showed increased slow-wave sleep and decreased nocturnal awakenings without effects on other sleep parameters (Ancoli-Israel *et al.* 2011). Pimavanserin significantly reduced insomnia in a trial of major depressive disorder in which it was given as adjunctive therapy (Jha *et al.* 2020). 5-HT$_{2A}$ receptors may play an important role in sleep and wakefulness, and receptor antagonists have been investigated as potential hypnotics (Al-Shamma *et al.* 2010; Landolt and Wehrle 2009).

An open-label investigation of pimavanserin in patients with Parkinson's disease and major depressive disorder demonstrated that 60% of patients showed a greater than 50% reduction in depression rating scale scores, and 44% experienced remission of depressive symptoms (DeKarske *et al.* 2020). Further exploration of the effects of pimavanserin on mood changes in Parkinson's disease and other neurodegenerative diseases may be warranted.

Hallucinations and Delusions in Alzheimer's Disease Psychosis

Following its approval to treat PDP, pimavanserin was assessed in patients with hallucinations and delusions associated with Alzheimer's disease psychosis (ADP). In a double-blind, placebo-controlled, parallel-group trial, 181 nursing home residents with probable or possible Alzheimer's disease and psychosis were randomly assigned to receive pimavanserin (34 mg/day) or placebo (Ballard *et al.* 2018). The primary outcome was the difference between the drug and placebo in change from baseline on the Neuropsychiatric Inventory--Nursing Home version at week 6 of treatment. Sustained benefit and safety/tolerability were assessed through week 12. At week 6, there was a significant difference between drug and placebo in favor of pimavanserin ([?] 3.76 points for pimavanserin versus [?] 1.93 points for placebo). Patients in the placebo arm continued to improve during weeks 6-12, and the superiority of pimavanserin was not sustained to week 12. A secondary analysis of patients with more severe psychosis (i.e., those [$n = 57$] with baseline Neuropsychiatric Inventory--Nursing Home version psychosis scores > 12) found that this subgroup had a more robust treatment response, with 88.9% of patients receiving pimavanserin showing a scale score improvement of [?] 30% (vs. 43.3% [$P < 0.001$] of patients receiving placebo) and 77.8% (vs. 43.3% [$P = 0.008$]) showing [?] 50% improvement (Ballard *et al.* 2019). Patients who had at least a 50% reduction in psychosis scores experienced a concomitant significant reduction in agitation; those with less robust responses on psychosis measures had no significant reduction in agitation (Ballard *et al.* 2020). This finding suggests that pimavanserin can be used in the treatment of agitation when psychosis is present but may not be effective in reducing agitation when there is no associated psychosis. Pimavanserin is not approved by the FDA for the treatment of ADP or for the treatment of agitation.

Dementia-Related Psychosis

Pimavanserin was assessed in a clinical trial for dementia-related psychosis (DRP). The pivotal clinical trial of pimavanserin for PDP excluded patients with dementia; all participants had Mini-Mental State Examination (MMSE) scores higher than 20 (Cummings *et al.* 2014). A subsequent analysis showed that patients with greater cognitive impairment (MMSE scores of 21-24) had significantly greater reductions on the SAPS-PD than those with no cognitive changes or milder cognitive changes (MMSE scores of 25-30) (Espay *et al.* 2018). This finding suggested that pimavanserin could have a role in the treatment of hallucinations and delusions associated with PDP in patients with cognitive impairment.

A retrospective (~1 year) analysis comparing pimavanserin versus quetiapine in the treatment of psychosis in patients with Parkinson's disease and patients with Lewy body dementia found comparable efficacy for the two agents; however, compared with patients taking quetiapine, those taking pimavanserin showed lower discontinuation rates early in the treatment period and higher discontinuation rates later in the treatment period (Horn *et al.* 2019).

Study data suggesting pimavanserin's efficacy in the treatment of cognitive impairment in PDP, psychosis in Alzheimer's disease, and psychosis in dementia with Lewy bodies provided the foundation for the study of pimavanserin for DRP. HARMONY was a randomized discontinuation trial involving patients with five types of dementia with psychosis: Alzheimer's disease, Parkinson's disease with dementia, dementia with Lewy bodies, frontotemporal lobar degeneration, and vascular dementia (Foff *et al.* 2020; Tariot *et al.* 2021) (Figure 35-2). Eligible participants entered a 12-week open-label treatment period with pimavanserin. Other types of antipsychotic treatment were not allowed in the trial. Participants whose symptoms met the response criteria (a > 30% reduction in the SAPS hallucinations plus delusions total score, and a CGI-I score of 1 [very much improved] or 2 [much improved] at week 8 and at week 12) were randomly assigned to continue taking pimavanserin or to start taking placebo. During the open-label period, 70% of the participants had symptoms that met the response criteria at week 8, and 88% of those patients demonstrated a sustained response at week 12.

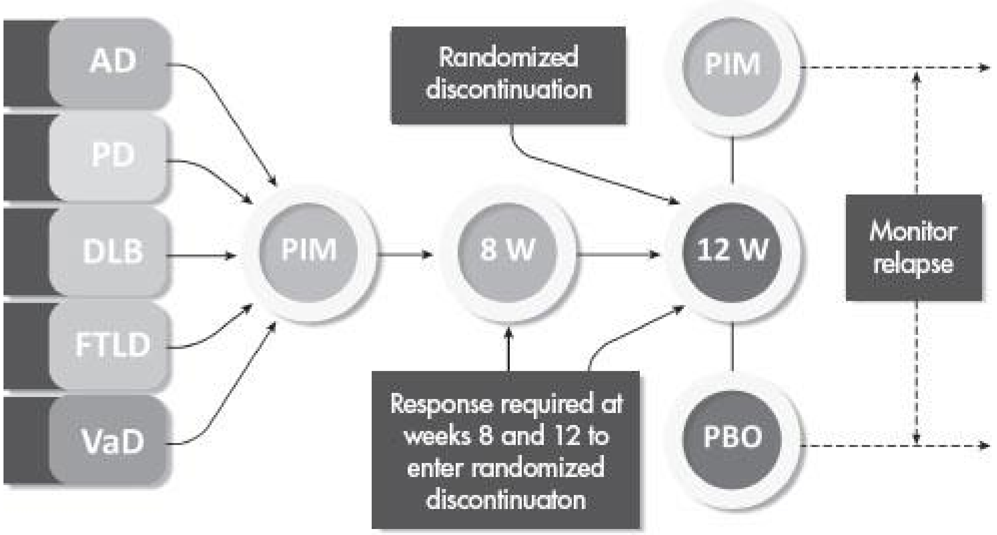
AD
PD
DLB
FTLD
VaD
PIM
8 W
12 W
PIM
PBO
Randomized discontinuation
Response required at weeks 8 and 12 to enter randomized discontinuaton
Monitor relapse

FIGURE 35-2. Randomized discontinuation trial of pimavanserin for the treatment of dementia-related psychosis: HARMONY (Tariot *et al.* 2021).

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; FTLD = frontotemporal lobar degeneration; PD = Parkinson's disease; PIM = pimavanserin; VaD = vascular dementia.

Source. Image copyright (c) J.L. Cummings; illustrator, Mike de la Flor, Ph.D.

The primary outcome of the HARMONY trial was time to relapse, defined as follows: 1) a > 30% worsening in the SAPS hallucinations plus delusions total score and a CGI-I score of 6 (much worse) or 7 (very much worse), 2) hospitalization due to DRP, 3) stopping of the study drug or withdrawal from the study due to lack of efficacy, or 4) use of other antipsychotics for the treatment of DRP. A prespecified interim analysis was based on the hazard ratio for relapse. The interim analysis revealed significant efficacy of pimavanserin over placebo, and the study was stopped early for definitive efficacy on the prespecified outcomes. The PDP group had a significant response to pimavanserin; other dementia groups had too few participants to allow assessment of efficacy within specific diagnoses (Tariot *et al.* 2021). Pimavanserin is not approved to treat DRP.

Major Depressive Disorder

Pimavanserin was assessed in a randomized, double-blind, placebo-controlled multicenter study of patients with major depressive disorder and an inadequate response to a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor (Fava *et al.* 2019). In stage 1 of a sequential parallel comparison design, patients were randomly assigned in a 3:1 ratio to placebo or pimavanserin added to ongoing selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor therapy; in stage 2 (week 5), placebo nonresponders were once again randomly assigned to placebo or pimavanserin for an additional 5 weeks. Significantly greater improvement with pimavanserin compared with placebo was observed on the 17-item Hamilton Rating Scale for Depression (Ham-D-17) total score and the Sheehan Disability Scale score. The difference between drug and placebo was evident at week 1. The most common adverse events with pimavanserin were dry mouth, nausea, and headache. A subanalysis of the anxiety/somatization factor of the Ham-D-17 showed a significant difference between drug and placebo in favor of pimavanserin. Patients with higher anxiety/somatization factor scores had more robust responses (Papakostas *et al.* 2020). However, two Phase III parallel-group trials of pimavanserin for treatment-resistant major depressive disorder failed to meet the primary outcome of a difference between drug and placebo on the Ham-D-17. Pimavanserin is not approved to treat major depressive disorder.

Negative Symptoms of Schizophrenia

Pimavanserin has been preliminarily assessed for efficacy in treating schizophrenia. In a randomized, double-blind 6-week trial, patients with chronic schizophrenia and a recent exacerbation of psychotic symptoms received pimavanserin (20 mg/day) as an

augmenting agent with low-dosage risperidone or haloperidol. The study showed that the combination of pimavanserin and low-dosage risperidone (2 mg/day) had the same efficacy as high-dosage risperidone (6 mg/day) and produced fewer side effects (weight gain, hyperprolactinemia). Pimavanserin combined with haloperidol 2 mg/day was equal in efficacy to haloperidol 2 mg/day without pimavanserin; however, participants taking the combination had fewer extrapyramidal effects. All treatment groups showed significantly greater reductions in the Positive and Negative Syndrome Scale total score compared with the placebo groups (Meltzer *et al.* 2012).

Open-label observations of pimavanserin for treatment-refractory hallucinations and delusions in patients with schizophrenia or schizoaffective disorder suggest that pimavanserin may be useful in this population (Nasrallah *et al.* 2019).

Use of pimavanserin in first-episode schizophrenia will be explored to determine whether there is a serotonergic subtype of schizophrenia that responds preferentially to 5-HT_{2A} inverse agonists/antagonists such as pimavanserin (Baltzersen *et al.* 2020; Nasrallah *et al.* 2019).

Pimavanserin is being assessed in a treatment trial for negative symptoms of schizophrenia (Krogmann *et al.* 2019). The combination of antipsychotic efficacy and dopamine release in the limbic cortex and mesocortex makes pimavanserin an attractive candidate for this indication.

Pimavanserin is not approved for use in schizophrenia.

Side Effects and Toxicology

All antipsychotics have boxed and bolded warnings that elderly patients with DRP treated with antipsychotic drugs are at increased risk for death. The manufacturer's current label (Acadia Pharmaceuticals 2023) states that pimavanserin is not approved for treatment of patients with dementia who experience psychosis unless their hallucinations and delusions are related to Parkinson's disease. This cautionary labeling requires that clinicians be vigilant when using this medication for DRP (Mathis *et al.* 2017). The causes of death among dementia patients treated with antipsychotics have been variable and have not been mechanistically related to the receptor profiles of antipsychotic agents. A recent comparison of mortality in patients with Parkinson's disease treated with pimavanserin or quetiapine found fewer deaths among those receiving pimavanserin (Mosholder *et al.* 2020); this suggests that pimavanserin may be less likely than other antipsychotics to increase mortality rates, but additional studies are needed.

Pimavanserin prolongs the cardiac QT interval, and its use should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval, including antiarrhythmics (e.g., quinidine, procainamide, amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin) (Caraci *et al.* 2020). Pimavanserin should be avoided in patients with a history of cardiac arrhythmias or with other conditions--such as symptomatic bradycardia, hypokalemia or hypomagnesemia, or congenital prolongation of the QT interval--that may increase the risk of torsades de pointes and/or sudden death (Acadia Pharmaceuticals 2023).

Common adverse reactions to pimavanserin with an incidence [?] 5% and at least twice the rate observed in a placebo group include peripheral edema (7% of patients taking pimavanserin 34 mg/day vs. 2% of those taking placebo) and confusional state (6% of patients taking pimavanserin 34 mg/day vs. 3% of those taking placebo) (Acadia Pharmaceuticals 2023).

Drug-Drug Interactions

Pimavanserin's effect on the QT interval suggests possible adverse drug interactions with antiarrhythmics (including quinidine, procainamide, amiodarone, and sotalol) and antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine) or antibiotics (e.g., gatifloxacin, moxifloxacin) that may induce QT prolongation (Acadia Pharmaceuticals 2023). Pimavanserin is metabolized through the CYP450 hepatic enzyme system. Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, clarithromycin, indinavir) may increase pimavanserin levels, requiring a reduction in dosage (the current recommendation is to reduce the dosage to 10 mg once daily) to avoid toxicity. Strong or moderate CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) may reduce pimavanserin levels, decreasing its efficacy and requiring a compensatory increase in dosage (Acadia Pharmaceuticals 2023); concomitant use of pimavanserin is not recommended with these agents.

Conclusion

Pimavanserin is a selective 5-HT_{2A} inverse agonist/antagonist approved to treat PDP. In clinical trials, it reduced hallucinations and delusions associated with PDP and ADP. Pimavanserin occupies a unique niche in the repertoire of neuropsychiatric agents as the only drug approved to treat psychosis in any neurodegenerative disorder. Pimavanserin is given in a single dose of 34 mg/day. It has a long half-life of approximately 55-60 hours. It can produce QT interval prolongation and should not be given to patients receiving drugs that may prolong the QT interval or to patients with a history of arrhythmias or QT prolongation. Pimavanserin may confer sleep benefits. It is being explored for other indications, including ADP and negative symptoms of schizophrenia.

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CHAPTER 36

Management of Psychiatric Medication-Induced Movement Disorders

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Acute and chronic movement disorders are a common side effect of medications used to treat psychiatric conditions. Antipsychotic medications that block dopamine D_2 receptors are recognized for this feature. Other psychiatric medications, including those that do not block dopamine receptors, can also cause clinically significant motor side effects, particularly tremor, and warrant consideration in the differential diagnosis of acquired abnormal movements. Regardless of the offending agent, treatment of medication-induced movement disorders relies on an awareness of which medications have this potential, characterization of the abnormal movements and the timing of their onset, and knowledge of pharmacological and nonpharmacological treatments.

This chapter addresses evaluation and management of movement disorder side effects caused by antipsychotic and other psychiatric medications. Common and familiar to most clinicians, the acute, subacute or chronic, and tardive motor syndromes induced by dopamine D_2-receptor blocking (DRB) antipsychotics provide a framework for describing the clinical phenomena of the different motor syndromes, conducting a differential diagnosis that includes the range of psychiatric and nonpsychiatric medications or other medical explanations, and initiating treatment. Because these iatrogenic movement disorders are underrecognized and can be associated with distress, falls, confusion, injuries, and harmful prescribing cascades, the above approach informs prescribing practices that mitigate risk for and manage drug-induced movement disorders.

History

Occurrence of abnormal movements as a side effect of psychiatric medications is inseparable from the early development of agents used to treat psychosis. This background is detailed in Chapter 25 ("Classic Antipsychotic Medications"). Notably, the terms used to describe drug-induced movement disorders and their inciting drugs have influenced drug development and patient care. In 1952, the discovery of chlorpromazine's antipsychotic effects (Delay and Deniker 1952; Laborit *et al.* 1952) was associated with recognition of its parkinsonian side effects (i.e., rigidity, bradykinesia, and tremor). In 1954, drug-induced parkinsonism (DIP) was formally described in patients treated with chlorpromazine and reserpine, a second-line antihypertensive agent that blocks vesicular monoamine transporter 2 (VMAT2) and results in monoamine depletion (Bergouignan and Regnier 1954; Steck 1954). In 1955, after Delay and Deniker proposed the term *neuroleptic* to the French Academy of Medicine to refer to the neurological side effects of parkinsonism, affective indifference, and emotional neutrality, chlorpromazine and other drugs producing similar effects were classified as neuroleptics, from the ancient Greek word meaning "one that grips the nerve" (Fielding and Lal 1978). A few years later, in 1959, descriptions of *tardive syndromes* (i.e., the long-term motor side effects from so-called neuroleptic drugs) were published (Lopez-Munoz *et al.* 2005; Sigwald *et al.* 1959). Although psychiatric medications other than these agents were subsequently found to cause movement disorders (Table 36-1), the prevailing focus has been on the role of this original group of DRB antipsychotic and monoamine-depleting agents (Blanchet and Kivenko 2016) in inducing abnormal movements.

TABLE 36-1. Medications known to cause movement disorders

Type of movement disorder	Neuropsychiatric medications	Other medications
Acute dystonic reactions	DRB antipsychotics	DRB antiemetic/promotility agents (e.g., clebopride, metoclopramide, prochlorperazine, promethazine)
	SSRIs	Antimalarial agents (e.g., quinine)
	Mood stabilizers or antiepileptics (e.g., carbamazepine, phenytoin, valproate)	Albendazole
	Opioids	Cetirizine
	Methylphenidate	Foscarnet
	Rivastigmine	Anesthetics (e.g., propofol, sevoflurane)
Gabapentin		

Note. DRB = dopamine D_2-receptor-blocking; MAOIs = monoamine oxidase inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.
Source. Adapted from Duma and Fung 2019; Friedman 2020; Zhou *et al.* 2022.

Type of movement disorder	Neuropsychiatric medications	Other medications
Akathisia	DRB antipsychotics	DRB antiemetic/promotility agents
	Antidepressants (SSRIs > SNRIs, MAOIs, TCAs)	DRB calcium channel blockers (e.g., cinnarizine, flunarizine)
	Mood stabilizers or antiepileptics (e.g., carbamazepine, pregabalin, valproate)	Azithromycin
	Buspirone	Sumatriptan
	Lithium	Methyldopa
	Tetrabenazine	Levodopa
	Dopamine agonists	
Tremor (nonparkinsonian)	Antidepressants (SSRIs > TCAs)	DRB antiemetics
	Lithium	Thyroid hormone replacement
	Mood stabilizers or antiepileptics (e.g., carbamazepine, phenytoin, valproate)	Bronchodilators
	Withdrawal from benzodiazepines, ethanol, or opiates	Amiodarone

Note. DRB = dopamine D_2-receptor-blocking; MAOIs = monoamine oxidase inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Source. Adapted from Duma and Fung 2019; Friedman 2020; Zhou *et al.* 2022.

Type of movement disorder	Neuropsychiatric medications	Other medications
	Immunosuppressants (e.g., cyclosporine, tacrolimus)	
Parkinsonism	DRB antipsychotics	DRB antiemetics
	Dopamine-depleting agents (e.g., deutetrabenazine, reserpine, tetrabenazine, valbenazine)	DRB calcium channel antagonists (e.g., cinnarizine, flunarizine)
	Mood stabilizers or antiepileptics (e.g., lamotrigine, levetiracetam, phenytoin, pregabalin, valproate)	Chemotherapy drugs (e.g., adriamycin, arabinoside, cyclophosphamide, cystosine, doxorubicin, etoposide, paclitaxel, vincristine)
	Antidepressants (SSRIs, MAOIs)	
Lithium		
Tardive movements	DRB antipsychotics	DRB antiemetic/promotility agents

Note. DRB = dopamine D_2-receptor-blocking; MAOIs = monoamine oxidase inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Source. Adapted from Duma and Fung 2019; Friedman 2020; Zhou *et al.* 2022.

Type of movement disorder	Neuropsychiatric medications	Other medications
SSRIs (if prior use of antipsychotics)		
Myoclonus and asterixis	Antidepressants--all types Clozapine, other antipsychotics	--
Mood stabilizers or antiepileptics (e.g., gabapentin, lamotrigine, topiramate, valproate)		

Note. DRB = dopamine D_2-receptor-blocking; MAOIs = monoamine oxidase inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.
Source. Adapted from Duma and Fung 2019; Friedman 2020; Zhou *et al.* 2022.

The hypothesized relationship between the therapeutic effect of antipsychotic agents and the drug-induced neuroleptic syndrome, and parkinsonism specifically, is also noteworthy. Some (Flugel 1953; Haase 1954) contended that these neurological side effects were necessary for the antipsychotic efficacy of chlorpromazine. Accordingly, clinical potency was titrated to occurrence of DIP in some drugs developed to treat psychosis (Lopez-Munoz *et al.* 2005). This theory, debated throughout the 1950s and 1960s (e.g., Brooks 1956), ultimately was not substantiated by a double-blind, placebo-controlled trial by Guttmacher (1964) showing comparable antipsychotic efficacy and a lower incidence of neurological side effects with thioridazine as compared with chlorpromazine and fluphenazine. Multiple subsequent studies further showed that antipsychotics at dosages greater than the "neuroleptic threshold" (i.e., the lowest dosage that causes a clinically detectable increase in signs of a hypokinetic-rigid syndrome) are likely to increase motor symptoms but confer no additional therapeutic benefit (Angus and Simpson 1970; Baldessarini *et al.* 1988; McEvoy *et al.* 1991). Nonetheless, the perception that the drug-induced neuroleptic syndrome was a marker of antipsychotic efficacy persisted and influenced clinical practice. For example, when clozapine was first synthesized in 1959, it was not considered a potential antipsychotic agent because it did not induce motor side effects. Later, despite clozapine's demonstrated efficacy as a treatment for schizophrenia, its release for clinical use in Europe was delayed until 1972 because of the popular belief that antipsychotic effects were not possible without associated parkinsonism (Hippius 1989; Lehmann and Ban 1997).

Clinical attention to psychiatric medication-induced movement disorders continues to be influenced by the nomenclature used for antipsychotic medications (King and Voruganti 2002). Most notable is the impact of the term *neuroleptic*, which refers to an adverse side effect rather than a beneficial pharmacological effect. Yet, the term *neuroleptic* is often used to denote antipsychotic medications in general, and antipsychotics that cause parkinsonism in particular. These agents, also known as classic, traditional, or conventional antipsychotics, are called first-generation antipsychotics (FGAs) in this chapter. A demand for safer and more tolerable antipsychotics led to development of the second-generation antipsychotics (SGAs), which were also called atypical or novel antipsychotics because of their lower propensity to cause abnormal movements. Although different mechanisms of action influence the relative risk for each SGA to induce movement abnormalities, a general perception of their improved safety was associated with a threefold increase in SGA prescribing, including for off-label uses in vulnerable populations such as the elderly and children and by nonpsychiatric clinicians (Friedman 2012). These prescribing patterns underscore the relevance of standardized baseline and ongoing follow-up assessments to prevent and manage drug-induced movement disorders (American Psychiatric Association 2021; Pringsheim *et al.* 2018).

A host of psychiatric and nonpsychiatric drugs, with and without influences on dopamine, can cause abnormal movements (see Table 36-1). When psychiatric patients develop abnormal movements, especially parkinsonism, causal agents aside from FGAs and SGAs can be overlooked when the focus is on "neuroleptic" drugs (Chouksey and Pandey 2020). Valproate, lithium, and DRB antiemetic agents (e.g., metoclopramide, promethazine) are common examples. Antiepileptic drugs, used to treat seizures, chronic pain, and primary psychiatric conditions, are associated with a broad range of abnormal movements that overlap with psychiatric symptoms or antipsychotic-induced movements (e.g., tics with lamotrigine; parkinsonism with valproate and gabapentinoids) (Pacheco-Paez *et al.* 2020; Zhou *et al.* 2022).

Finally, movement disorder specialists argue that the term *extrapyramidal* is obsolete, contending that its inexact and global use as both a descriptor and a cause of abnormal movement phenomena in psychiatric patients discourages accurate diagnosis and appropriate treatment (Obeso 2019). That is, the synonymous and interchangeable use of the terms *extrapyramidal drugs, movements, syndromes, and disorders* in connection with DRB antipsychotics, basal ganglia motor networks, and effects on basal ganglia function restricts consideration of the role of other psychiatric and nonpsychiatric medications and motor systems in drug-induced motor phenomena. Given that many psychiatric drugs cause abnormal movements, a preferred approach is to describe, rather than explain, the observed clinical motor phenomena (e.g., tremor at rest, akathisia, dystonia) and their timing; pursue the differential etiologies, including primary or drug-induced conditions; and implement appropriate interventions. Such an approach facilitates serial evaluations and consideration of whether the observed drug-induced movements represent a de novo movement disorder versus an exacerbated primary movement disorder, such as Parkinson's disease, essential tremor, or cervical dystonia. Notably, offending medications may "unmask" signs and symptoms of a primary movement disorder that is emerging but not yet diagnosed. In the assessment of movement disorders, the extrapyramidal system can be best conceptualized as referring to all of the various neural networks that modulate motor movement and coordination and that are distinct from the pyramidal system (i.e., the corticospinal and corticobulbar pathways that pass through the medullary pyramids and directly innervate lower motor neurons). Accordingly, to avoid imprecision and promote discovery, the term *extrapyramidal* is no longer accepted in the journal *Movement Disorders* (Obeso 2016).

Movement Disorder Phenomenology

A systematic approach to treatment of psychiatric medication-induced movement disorders starts with clarification of the chronological onset of the movements relative to the time of ingestion of or exposure to the potential offending agent and characterization of the abnormal movements. This is accomplished by eliciting the history of the onset and course of the movements and conducting a physical examination. Information on current and remote medications and family history, also key elements, often require data from other sources.

Timing of Abnormal Movements

Drug-induced movement disorders are categorized according to the timing of the onset and resolution of the abnormal movements relative to the timing of exposure to the medication. *Acute disorders* appear within minutes to days of drug exposure and can be life threatening. Examples are acute dystonic reactions, akathisia, and tremor. This chapter does not discuss serotonin syndrome, neuroleptic malignant syndrome (NMS), or the akinetic crisis of Parkinson's disease, which can also occur with psychiatric

medications and involve abnormal motor movements. *Subacute disorders*, exemplified by DIP, occur days to weeks after drug exposure. Some acute disorders can also have a subacute onset; levodopa-induced dyskinesia, a subacute condition that is not addressed in this chapter, is an example. Abnormal movements that persist for several months while an individual is taking an offending agent are considered *chronic disorders*. Diagnosis of a *tardive syndrome or disorder* is made only in the context of known exposure to DRB agents. Tardive disorders are defined as abnormal movements that persist after discontinuation of any DRB medication or that subside when the DRB medication dosage is increased. Onset tends to occur after prolonged exposure (typically defined as after 3 months, or after 1 month for adults older than 60 years). However, movements may not be observed for several months to years of ongoing exposure. The most common tardive movement disorder, referred to as "classic tardive dyskinesia" (TD), involves oral-buccal-lingual (OBL) dyskinetic movements. Other tardive movement phenomena may be present, with or without concurrent TD. Other relatively common tardive syndromes include tardive dystonia, tardive akathisia, and withdrawal-emergent syndrome. Withdrawal dyskinesias or akathisias occur after medication discontinuation or dosage reduction and usually resolve after about 6 weeks. Movements still present after that time likely represent a tardive condition.

Clarification of the timing of exposure to the drug relative to the timing of onset and resolution of drug-induced movements is essential for accurate diagnosis and effective treatment. A single cross-sectional examination and patient interview may provide inadequate information. Serial motor evaluations, collateral informants, and pharmacy records provide critical data for diagnosis, especially for patients who have been exposed to offending medications for longer durations. Notably, acute, subacute, and chronic *medication-induced abnormal movements* should subside and resolve when the offending drug is removed or reduced, even if full resolution of the movements occurs gradually after cessation of the medication. By contrast, *tardive syndromes* emerge or persist when the offending drug is discontinued or reduced and subside or diminish when the dosage is increased.

Types of Abnormal Movements

Abnormal motor phenomena, regardless of etiology, are classified as either hyperkinetic or hypokinetic, and their related movement disorder syndromes fall into two broad categories: hyperkinetic and akinetic-rigid conditions. In *hyperkinetic* disorders, there are excessive involuntary movements, also called *dyskinesias*, that are distinguished from one another by the presence or absence of rhythmic and stereotyped movements. Tremor, dystonia, chorea, tics, and myoclonus are the most common types of dyskinesias. Rhythmic hyperkinetic movements suggest a tremor or tremor-like disorder. Tremors are further characterized by how they occur, such as at rest, with certain postures, or during active movements. Stereotyped movements, by definition, occur repeatedly but are not rhythmic. Dystonias are slow stereotyped movements, whereas motor tics present as rapid stereotyped movements. Hyperkinetic movements that lack both rhythmicity and stereotypy include chorea, ballismus, and myoclonus; these are distinguished by their different speeds.

Hypokinetic or akinetic-rigid syndromes are characterized by their paucity of spontaneous voluntary movements. *Hypokinetic* phenomena include a reduction in the amplitude and speed of movement (bradykinesia), a lack of movement or an impairment

in the ability to initiate movement (akinesia), and increased muscle tone (rigidity). The akinetic-rigid disorders are exemplified by Parkinson's disease and other causes of parkinsonism. Although parkinsonism refers to an akinetic-rigid syndrome, hyperkinetic phenomena, such as a tremor, may be concurrent and remain classified as hyperkinetic movements in that context.

Acute Medication-Induced Movement Disorders

Acute Dystonia and Acute Dystonic Reactions

Presentation

Acute dystonic reactions involve abnormal muscle contractions (increased muscle tone) and postures that result in sustained involuntary twisting or repetitive patterned movements. The body regions most often affected are ocular muscles (oculogyric crisis or blepharospasm) or face, jaw, tongue, or neck muscles (torticollis or retrocollis), and, less often, the trunk or limbs (limb dystonia). The sustained muscle contractions cause pain, discomfort, and anxiety. Presentation varies according to the affected muscle group (e.g., trismus; a thickened, tense tongue or throat; dystonic mouth opening; grimacing; dysarthria; swallowing difficulties; unusual neck turning, limb postures, or truncal twisting). A few fingers may be the only affected body part, or the dystonia may be generalized, as with opisthotonos. Because presentations of acute dystonia are protean and can be bizarre, an episode can be mistaken for a functional movement disorder.

Most acute dystonic reactions occur soon after initiating treatment, typically following a single dose or an increase in the dosage of an offending agent. The onset can occur within a few minutes of ingestion but usually develops over a period ranging from a few hours to as long as 2-5 days after initiating or raising the dosage of the inciting medication or after reducing the dosage of a medication used to treat or prevent acute dystonia. In comparison with earlier symptom onset, emergence of dystonic phenomena after 10 days is more likely to represent tardive dystonia or another cause of dystonia. Other causes of dystonia should be considered if the acute dystonic reaction fails to respond to acute treatment, indicated below.

Acute laryngeal dystonia can result in life-threatening airway obstruction and requires emergency treatment. Its presentation involves stridor, clutching the throat, dysphonia, respiratory distress, and dysphagia. The population at greatest risk for acute dystonic reactions is young people--including infants, children, and adults who are younger than 40 years and have psychosis. Both genders are susceptible, but development of acute dystonia is more likely in adult males than females in most studies (van Harten *et al.* 1999). A history of acute dystonic reactions confers an increased risk for subsequent events, as does recent cocaine use, hypocalcemia, dehydration, or hypoparathyroidism. Acute dystonic reactions rarely develop in the elderly (van Harten *et al.* 1999).

Offending Medications

Any DRB medication can cause acute dystonia. The most common causes in a psychiatric population are antipsychotics. Observed rates are higher with FGAs (17% of patients treated with haloperidol) than with SGAs (< 2% of patients treated with quetiapine or clozapine) (Martino *et al.* 2018). Other psychiatric medications or drug classes reported as causing acute dystonic reactions include selective serotonin reuptake inhibitors (SSRIs), opioids, methylphenidate, rivastigmine, and gabapentin. Various other DRB medications (e.g., antiemetic, anti-infective, and antiepileptic agents) can also cause acute dystonia (see Table 36-1).

The mechanisms underlying acute dystonic reactions are unknown. The increased risk for acute dystonic reactions associated with high-potency DRB antipsychotics, the lower risk with lower-potency antipsychotics, and the prompt relief of acute dystonic reactions with anticholinergic medications all suggest a relationship between relative dopamine and cholinergic blockade.

Treatment

Acute dystonic reactions cause significant physical discomfort and distress that is often followed by anxiety about taking the offending medication and related medications in the future. Even with SGAs, there is always risk at the individual patient level. Clinicians should be vigilant for this potential complication to facilitate its prompt management and to avoid deleterious effects on medication adherence. Patients and families, especially those in high-risk groups, should be informed prior to starting a potentially offending agent of the risk for acute dystonic reactions and the need to monitor for and manage them. In general, once an acute dystonic reaction occurs, the offending medication is discontinued and a different agent, as indicated, is substituted. The offending drug should be avoided thereafter, as there is a risk for recurrent acute dystonic reactions.

Management of an acute dystonic reaction requires immediate intervention. In inpatient or emergency settings, intramuscular anticholinergic benztropine (1-2 mg) provides rapid relief of acute dystonic reactions, usually within 20 minutes. Second and third injections, administered every 30 minutes, may be needed. Given that parenteral benztropine has a short half-life, acute dystonic reactions can recur within several hours and require additional dosing. Acute treatment should be followed by a brief course of an oral anticholinergic drug for 4-7 days to prevent recurrence (Park *et al.* 2017). To prevent recurrent acute dystonic reactions, the prophylactic dosage should then be reduced gradually. Potential adverse effects of anticholinergics are detailed below.

Intravenous anticholinergic treatment is indicated when the dystonia is life-threatening (i.e., with laryngeal stridor, risk of joint dislocation). Clonazepam 0.5-4 mg may be indicated when oculogyric crisis fails to respond to anticholinergic medications.

Diphenhydramine (50-100 mg IM or IV) can be used emergently, although it is less effective than the immediate relief provided by benztropine (2 mg IM) (Lee 1979). Outpatients who experience acute dystonic reactions should be advised to self-administer oral diphenhydramine and seek further medical care. Benzodiazepines can also be considered but are less effective than anticholinergics. Botulinum toxin injections have been suggested for drug-induced stridor with laryngeal dystonia (Burkhard 2014) as well as for prophylaxis in patients subject to relapse of laryngeal dystonia (Marano *et al.* 2016).

Prophylactic Treatment of Acute Dystonic Reactions

When an antipsychotic medication is started or continued, acute dystonic reactions can be prevented by using anticholinergic drugs during the first 7 days of treatment

(Burkhard 2014). Based on the patient's compilation of risk factors (e.g., age, gender, antipsychotic potency, dosage), prophylactic anticholinergic medication (e.g., benztropine 2 mg two to three times daily) can be added to treatment with the antipsychotic medication. Amantadine 100 mg once to three times daily is used as an alternative when anticholinergics are not tolerated. As above, prophylactic treatment should be continued for 7 days and then tapered slowly to avoid inducing an acute dystonic reaction. High-potency antipsychotic drugs can be started at low dosages to reduce the risk of acute dystonic reactions (van Harten *et al.* 1999). Prolonged or routine use of prophylactic agents is discouraged (World Health Organization 1990).

Acute Akathisia

Presentation

The term *akathisia*, meaning "inability to sit," was first used by Ladislav Haskovec, a Czechoslovakian neuropsychiatrist (Brune and Sachdev 2002), in 1901 to describe psychomotor restlessness in unmedicated patients regarded as having "hysteria" or "neurasthenia" (Sachdev 1995). In 1960, akathisia, as a medication-induced condition, was reported in patients taking phenothiazine antipsychotics (Salem *et al.* 2017). While its association with antipsychotic medications is well recognized, akathisia also occurs as a side effect of numerous psychiatric and nonpsychiatric medications, including antidepressants, dopamine-blocking antiemetics, calcium channel blockers, and antiepileptic agents. For this reason, akathisia often goes unrecognized, especially in medical and geriatric settings where individuals are prescribed antipsychotic medications for agitation, delirium, or psychosis in the context of dementia (Forcen *et al.* 2016) or in oncology, neurology, or primary care settings (Akagi and Kumar 2002; Rissardo *et al.* 2021). It is also important to distinguish akathisia from restless legs syndrome. The latter generally manifests during times of rest or sleep and is treated with dopamine agonists, which could exacerbate psychosis and lead to higher dosages of antipsychotics and worse akathisia (Bratti *et al.* 2007). Any acute onset of restlessness and agitation should prompt consideration of akathisia and a review of medications for the recent initiation or dosage increase of drugs or prescribing cascades known to cause akathisia.

Unlike the other common medication-induced movement disorders, akathisia has prominent subjective and objective components. Typically, there is a complaint of a mounting or excessive internal restlessness or tension that is accompanied by a strong urge to move around, such as when sitting in a class or standing in a line (Pringsheim *et al.* 2018). The experience of akathisia can be entirely subjective, without observed abnormal movements. However, for many patients, movement provides some relief of their symptoms.

The types of movements constituting akathisia vary across individuals; manifestations of akathisia can include inability to sit, stand, or lie still and usually (although not exclusively) involves the legs. Movements include pacing, leg swinging or crossing, marching in place, shifting from one foot to the other, shaking, rocking the legs or trunk back and forth, rubbing the face, fidgeting, scratching, or moaning. The movements tend to be bilateral and symmetrical. Pseudoakathisia, a debated entity classified as a form of chronic akathisia (Havaki-Kontaxaki *et al.* 2000), involves objective signs of akathisia in the absence of awareness of internal restlessness.

One challenge in diagnosing akathisia is that some patients, both adults and children, are unable to find words to describe their symptoms (Akagi and Kumar 2002). Vague and nonspecific complaints of inner tension, anxiety, an inability to relax, nervousness, restlessness, discomfort, and so forth, accompanied by irritability, agitation, and constant motion, may be misattributed to a primary psychiatric condition or a new onset of a mood or psychotic disorder. In the context of failure to recognize a medication-induced disorder, offending medications (e.g., antipsychotics, antidepressants) might be initiated or increased, thereby further exacerbating the akathisia symptoms (Pringsheim *et al.* 2018). The physical experience of inner restlessness often gives rise to emotional distress, anxiety, or dysphoria; acute, severe, or chronic cases of akathisia can lead to self-harm, suicidality, aggression, or violence. Distress associated with akathisia also contributes to medication nonadherence.

Onset of acute akathisia is typically rapid, with symptoms usually appearing within a few days to a week of starting--or increasing the dosage of--the offending medication. In published diagnostic criteria for akathisia (Bratti *et al.* 2007), acute akathisia requires symptom onset within 6 weeks of drug initiation or dosage increase (plus the absence of reduction or discontinuation of a therapeutic agent within the 2 weeks before symptom onset). For the diagnosis of chronic akathisia with acute onset, symptoms must have persisted for more than 3 months. For tardive akathisia (discussed further in the later section "Tardive Dyskinesia and Tardive Syndromes"), symptom onset must have occurred at least 3 months after starting an antipsychotic agent; the diagnosis also requires the absence of a change in antipsychotic dosage or medication within 6 weeks before symptom onset and the absence of a reduction or discontinuation of another therapeutic agent in the 2 weeks before symptom onset. First-time use of an antipsychotic and a rapid increase in antipsychotic dosage appear to confer greater risk for akathisia than does simply taking a higher dosage of an offending agent. Other than rare reports of clozapine-induced akathisia, which is more likely to occur in children and adolescents than in adults (Gogtay and Rapoport 2008; Grover and Sahoo 2015), there is no apparent impact of age or sex on the prevalence of antipsychotic-induced akathisia (Laoutidis and Luckhaus 2014).

Offending Medications

Akathisia is most prevalent as an adverse effect of treatment with an antipsychotic, particularly a high-potency FGA (e.g., haloperidol, fluphenazine). In community-based samples, the overall prevalence of akathisia in individuals with schizophrenia is around 20% (Pringsheim *et al.* 2017). Meta-analyses show a lower prevalence of akathisia with intermediate-and low-potency FGAs. Certain SGAs (e.g., aripiprazole, asenapine, paliperidone, ziprasidone) are associated with higher rates of akathisia (Forcen *et al.* 2016). Akathisia risk is also higher for patients receiving two different SGAs than for those receiving an SGA plus an FGA. Compared with SGA monotherapy, SGA polytherapy confers a threefold higher risk of akathisia (10.9% vs. 34.2%) (Salem *et al.* 2017). Akathisia can also occur with clozapine and (as noted earlier) appears to have a relatively greater incidence in children than in adults (Gogtay and Rapoport

2008; Gogtay *et al.* 2002). Lithium-induced akathisia is also described (Demir *et al.* 2021).

Table 36-1 lists psychiatric and nonpsychiatric medications that are also reported to cause akathisia. Akathisia should be distinguished from psychomotor activity related to anxiety, agitation, tics, classic TD, or restless legs syndrome (Salem *et al.* 2017).

Treatment

The first principles in management of akathisia are risk mitigation strategies and monitoring for its potential occurrence. Patients and caregivers should be informed that akathisia is a potential medication-induced side effect and should be educated about its features. These should be distinguished from phenomena associated with the primary psychiatric condition or distress that arises in the context of a primary medical condition. The contribution of a drug-induced akathisia to the clinical picture is worthy of consideration on medical units, where restlessness, distress, and anxiety might be misattributed to delirium or existential concerns (e.g., in a patient with dementia or after a diagnosis of cancer). A best practice is to use a validated scale to assess patients for signs and symptoms before starting and while titrating the dosage of a potentially offending agent. The Barnes Akathisia Rating Scale has established reliability, validity, and utility for this purpose (Pringsheim *et al.* 2017). When prescribing antipsychotics, polypharmacy, rapid dosage escalation, and high-dosage treatment should be avoided when there is no evidence for clinical effectiveness, even if there is no obvious clinical harm.

Once evidence for akathisia is established, offending medications should be tapered and, if clinically appropriate, discontinued or substituted with an alternate medication or other treatment approach. When long-term use of the offending medication class is necessary, efforts should be made to taper and discontinue the specific medication, and, if the patient is already on monotherapy, switch, if possible, to an agent with an overall lower risk profile for akathisia, such as clozapine, olanzapine, or quetiapine in the case of antipsychotic treatment (Pringsheim *et al.* 2017). Clozapine should be considered for intractable or refractory akathisia (Salem *et al.* 2017).

Clinical trials of anti-akathisia medications have focused mainly on use of b-blockers and are limited to individuals taking antipsychotic medications (Pringsheim *et al.* 2018). A systematic review on treatment of antipsychotic-induced akathisia reported on seven published placebo-controlled trials evaluating propranolol, a nonselective b-adrenergic receptor antagonist (Pringsheim *et al.* 2018). For children and adults with antipsychotic-induced akathisia, propranolol is generally the first-line treatment barring individual medical contraindications or precautions regarding its use (e.g., asthma, orthostatic hypotension, bradycardia, drug-drug interactions).

A prudent starting dosage for propranolol is 5-10 mg two to three times a day with titration as needed for symptomatic improvement. Relative to placebo in controlled trials involving patients with schizophrenia, propranolol showed greater efficacy at dosages ranging from 20 mg/day to 120 mg/day. Both nonselective (b_1 and b_2 antagonism) and selective (b_1 antagonism) b-blockers are also reported to be efficacious. For once-daily dosing, the usual starting dosage of b_1-selective atenolol is 50 mg/day. Betaxolol may be the b-blocker of choice for patients with lung disease and smokers because of its b_1 selectivity at lower dosages (5-10 mg/day). Limited data support use of clonidine, a selective a_3-adrenergic agonist, up to 0.15 mg/day, as an alternative option for akathisia, although its associated side effects of sedation and hypotension can be problematic (Fleischhacker *et al.* 1990).

More recently, postsynaptic serotonin 5-HT_{2A} receptor antagonists (e.g., ritanserin, cyproheptadine, trazodone, mianserin, mirtazapine) have entered the armamentarium of potential anti-akathisia agents (Poyurovsky and Weizman 2020). The most robust evidence supports use of mirtazapine 7.5-15.0 mg once daily as a long-term anti-akathisia treatment when propranolol is contraindicated, not effective, or not tolerated (Pringsheim *et al.* 2018). A meta-analysis of data from placebo-controlled trials of mianserin, mirtazapine, and trazodone showed a positive effect for all three 5-HT_{2A} antagonists as a group (RR = 7.10, 95% CI = 3.08-16.40; $P < 0.0001$) (Laoutidis and Luckhaus 2014). However, mirtazapine showed a more favorable safety and side-effect profile (sedation, weight gain) when used with antipsychotics, in contrast to mianserin (15 mg/day) and trazodone (100 mg/day), which have adrenergic-blocking properties. Cyproheptadine 8-16 mg/day is an alternative option, although trial data are limited.

Several other agents have been evaluated or suggested as anti-akathisia agents. Two small short-term trials of oral vitamin B_6 600 mg/day or 1,200 mg/day versus placebo showed significant anti-akathisia effects. Short-term use (5 days) can be considered; long-term administration (> 12 months) of oral vitamin B_6 at dosages of 1,000 mg/day can result in a sensory neuropathy and is not recommended (Pringsheim *et al.* 2018). The antihistamine diphenhydramine, which also has potent anticholinergic properties, has not shown any consistent benefit for this indication and may worsen akathisia (Salem *et al.* 2017). Insufficient data support use of other medications evaluated as potential akathisia treatments. Dopamine agonists have limited utility, given their propensity to increase psychosis. An earlier study of amantadine suggested that it is probably not effective for treating akathisia (Fleischhacker *et al.* 1990). However, because a small number of patients have shown beneficial effects, amantadine 100 mg/day is recommended as a final option only after other interventions have failed (Poyurovsky 2010). Gabapentin and pregabalin, which can be effective for restless legs syndrome, are cited in case reports as benefiting as well as inducing akathisia, although these agents may improve tardive akathisia (Pringsheim *et al.* 2018; Salem *et al.* 2017). Sodium valproate showed no significant effect on akathisia and also increased parkinsonism (Friis *et al.* 1983).

Anticholinergics are not recommended as a treatment for akathisia, given their unfavorable effects on cognition, other adverse effects, and limited and inconsistent evidence for efficacy (Rathbone and Soares-Weiser 2006). For example, a small placebo-controlled trial of parenteral benztropine showed improvement in subjective symptoms of akathisia, but not in objective signs (Sachdev and Lonergan 1993). In a trial comparing an unusually high dosage of oral benztropine (6 mg/day) and propranolol (80 mg/day) against placebo, both drugs produced significant improvement in akathisia ratings relative to placebo (Adler *et al.* 1993a). In an earlier comparison trial, however, propranolol was more effective for antipsychotic-induced akathisia than was benztropine (up to 4 mg/day), which yielded a slight decrease in subjective akathisia ratings but no change in objective ratings (Adler *et al.* 1987). Observational reports suggest that anticholinergics may benefit individuals with both parkinsonism and akathisia, but cautious use is advised (Braude *et al.* 1983). A single case report described temporary resolution and diminution of all motor abnormalities after a course of electroconvulsive therapy (ECT) in a patient with antipsychotic-induced akathisia and parkinsonism that was not responsive to anticholinergic medications (Hermesh *et al.* 1992). Conversely, there are reports of worsening akathisia with ECT (Bakheit 1997).

Benzodiazepine agents do not reduce akathisia and are not recommended as a specific treatment. They may be indicated in the short term for severe anxiety or agitation

in patients also treated with propranolol. Oversedation is a significant risk when benzodiazepines are co-administered with mirtazapine, mianserin, or cyproheptadine.

Acute Medication-Induced Nonparkinsonian Tremor

Presentation

Drug-induced tremors can be vexing to diagnose. Some psychiatric medications, such as lithium and valproate, cause parkinsonism as well as nonparkinsonian tremors. Nonparkinsonian drug-induced tremors tend to resemble essential tremor and most often manifest as an enhanced physiological tremor that is lower amplitude (i.e., finer), faster (i.e., with higher-frequency oscillations [10 cycles per second]), affects both upper limbs, and emerges when maintaining a position against gravity (postural tremor), during voluntary movement (kinetic tremor), or both. A nonparkinsonian drug-induced tremor is most likely to be evident during intentional postures, such as when writing or holding a coffee cup. Usually, physiological tremors are not symptomatic or visible, except when enhanced by fatigue, anxiety, or an offending drug (Bhatia *et al.* 2018).

Drug-induced tremors are typically isolated tremor syndromes (i.e., tremor is the only abnormal sign), although other medical or neurological conditions may co-occur. The clinical history, tremor phenomena and other signs on exam, and further testing, as indicated, help distinguish a drug-induced tremor from other causes of tremor. As would be expected, acute drug-induced tremors are more likely to demonstrate a temporal relationship between drug ingestion and tremor onset, a dose-response relationship, absence of tremor progression, and normalization of enhanced tremor upon removal of the offending drug. Other etiologies of tremor should be excluded, such as Parkinson's disease, essential tremor, hyperglycemia, hyperthyroidism, cerebellar disease, or cerebral vascular lesions.

Drug-induced tremors begin soon after ingestion of the drug, after dosage escalation, or via drug-drug interactions when a new drug is added to an existing regimen. Other triggering factors for enhanced physiological tremor in the context of an offending drug include polypharmacy, caffeine use, metabolic conditions, anxiety or mood states, alcohol withdrawal, fever, or shivering when the ambient temperature is low (Factor *et al.* 2019).

Offending Medications

Nonparkinsonian tremor is a common side effect of many drugs (Baizabal-Carvallo and Morgan 2022). Common tremor-inducing psychiatric drugs include antidepressants, notably SSRIs and tricyclic antidepressants (TCAs), lithium, antiepileptics (especially valproate), bronchodilators, amiodarone, and immunosuppressants. A recent review of 97 patients with drug-induced movement disorders in a neurology practice found that postural hand tremor was the most common movement disorder in those exposed to non-DRB drugs (54%), especially antiepileptics and antidepressants. However, postural tremors were also present in the groups on only DRB agents (17%) and on both DRB and non-DRB drugs (40%) (Chouksey and Pandey 2020).

Lithium-induced nonparkinsonian tremor occurs in about 30% of patients, is more common in older individuals and men, and is reported as problematic by about one-third of patients who experience it. A lithium-induced tremor usually presents early in the course of treatment, necessitating consideration of other causes of tremor when the onset is later (Gitlin 2016). Although the tremor may improve over time with stable therapy, addition of other psychiatric drugs (e.g., SSRIs, TCAs, valproate) can exacerbate the movements. Lithium toxicity can also exacerbate these movements, causing the tremor to become more coarse, irregular, and severe, spreading to other body parts and accompanied by other signs of toxicity. Coadministration of DRB antipsychotics with lithium can result in a complex combined tremor syndrome of multiple etiologies. Lithium is also associated with drug-induced parkinsonism, akathisia, chorea, myoclonus, a cerebellar syndrome, and serotonin syndrome (Meneret *et al.* 2021). Coadministration of carbamazepine with lithium, such as when both are used as mood stabilizers, increases the risk for ataxia and hyperkinetic movements such as myoclonus or dystonia.

Valproate, like lithium, is frequently associated with a parkinsonian or a nonparkinsonian tremor (Meneret *et al.* 2021). Nonparkinsonian valproate-induced tremor is categorized as a form of enhanced physiological tremor. It affects up to 80% of patients taking valproate. Although this tremor is usually mild, nearly 25% of affected patients (who tend to be relatively older and female) have more severe tremor that causes significant functional impairment (Alonzo-Juarez *et al.* 2017). Because the tremor tends to be bilateral and symmetric, and to involve the upper extremities, it frequently resembles essential tremor, one of the most common idiopathic movement disorders (Alonso-Juarez and Baizabal-Carvallo 2018). By contrast, however, tremor occurrence tends to be dosage-related and associated with a longer duration of valproate treatment (Zhang *et al.* 2020). Some studies have reported that higher tremor amplitude is seen with immediate-release formulations than with controlled-release formulations of valproate, although these data are controversial (Baizabal-Carvallo and Morgan 2022). Valproate-induced tremor is also reported to present as a tardive tremor.

Treatment

The cornerstone of effective management is proactive clinical and functional assessment. Patients should be assessed for preexisting tremor, including an enhanced physiological tremor, and educated about the potential for drug-induced tremor prior to initiating medications known to induce tremor (Baizabal-Carvallo and Morgan 2022). In the absence of baseline and serial exams, causes other than drug-induced tremor must be considered. Interventions for a drug-induced tremor include dosage alterations and reductions, elimination of additive factors such as caffeine, cessation of the offending drug if feasible, or transition to an alternative agent. For most patients, the nonparkinsonian tremor improves with time and is not disabling. More severe or socially embarrassing tremors can warrant medications for management, but watchful waiting for a natural diminution of symptoms and management of triggers are important first steps to avoid polypharmacy and deleterious prescribing cascades.

When medication treatment is necessary, b-blockers are used most often for a nonparkinsonian drug-induced tremor. Although the recommended dosage range for treatment of tremor with propranolol is 20-320 mg/day, a dosage less than or equal to 120 mg/day is usually effective (Gitlin 2016). Case reports describe use of primidone

and vitamin B_6. Benzodiazepines may be used when anxiety contributes significantly to the tremor.

Subacute Medication-Induced Movement Disorders

Medication-Induced Parkinsonism

DIP, the second most common cause of parkinsonism after idiopathic Parkinson's disease in general population studies, is a significant source of morbidity. Severe antipsychotic DIP occurs with both FGAs and SGAs, contributes to nonadherence, and can lead to complete immobility, dysarthria, and dysphagia as well as secondary complications such as falls with injuries and pneumonia (Druschky *et al.* 2020). Older individuals with DIP have higher rates of falls, hospitalizations, and mortality than do younger persons (Wilson and MacLennan 1989). Given that early recognition is important, any new case of parkinsonism should prompt a thorough medication history. However, the true prevalence of DIP is unknown, as it is underrecognized, and epidemiological studies tend to include all types of parkinsonism without distinguishing DIP cases (Thanvi and Treadwell 2009). In a population-based study of 706 men and women ages 50-89 years in northern Italy, comprehensive diagnostic assessments by movement disorder specialists identified a high overall prevalence (*n* = 214 participants, 28.0% [95% CI 25.9-30.1]) of common movement disorders, including parkinsonism, tremor, dystonia, chorea, tics, and restless legs syndrome (Wenning *et al.* 2005). Among the 214 participants with movement disorders, 43 cases (20%) were regarded as drug-induced, yielding a DIP prevalence of 1.69% (1.06%-2.33%). In the group of 33 individuals taking long-term (> 6 months) antipsychotic treatment in the 5 years before study assessment, 16 (49%) developed movement disorders (7 with DIP, 5 with DIP plus dystonia, and 4 with dystonia) (Wenning *et al.* 2005).

Globally, more than half of individuals older than 60 years taking long-term antipsychotics are estimated to have DIP (Estevez-Fraga *et al.* 2018). Studies suggest that DIP may be present in up to 12% of community populations, with a higher incidence in older age groups (Savica *et al.* 2017; Wisidagama *et al.* 2021). In a 30-year (1976-2005) population-based study in Olmsted County, Minnesota, 108 individuals, among the 906 incident cases of parkinsonism, developed DIP in association with prescription of DRB or dopamine-depleting agents (Savica *et al.* 2017). This finding corresponds to an average annual incidence rate (age-and sex-standardized to the total 1990 population) of 3.8 per 100,000 person years for DIP relative to a rate of 33.5 for all types of parkinsonism. The prevalence and natural course of DIP in individuals with continued drug exposure are not known. Severe, chronic DIP appears to be uncommon. With ongoing antipsychotic treatment, DIP may resolve spontaneously, but in up to half of patients it persists or progresses over time (Fernandez *et al.* 2001).

Presentation

Parkinsonism is defined by the presence of at least two of the three cardinal motor features of Parkinson's disease--bradykinesia (including akinesia), tremor, and rigidity. Other features include postural instability, abnormal flexed or stooped posture, micrographia, and hypophonia. On cross-sectional exam, clinical characteristics of

DIP are phenomenologically indistinguishable from the akinetic-rigid syndrome of idiopathic Parkinson's disease. Even asymmetric motor signs, a defining feature of idiopathic Parkinson's disease, may be present in DIP. Bradykinesia and akinesia result in decreased or absent facial movements (*hypomimia*, or "masked face"), a reduced blink rate leading to a staring appearance, and a reduced rate of swallowing, which causes drooling because of pooling of saliva. Gait abnormalities include shortened stride with a normal or narrow base, reduced or absent arm swing, stooped posture, a shuffling and festinating gait, and *en bloc* turning. Rigidity is experienced as involuntary stiffness and inflexibility of the muscles of the limbs, shoulders, neck, or trunk. On examination, increased muscle tone is constant throughout range of motion ("lead-pipe" rigidity) when the limb is moved passively around the joint.

Tremor associated with DIP most often occurs in the resting state and with sustained postures. Typically, fingers or hands are involved, but the tongue, jaw, or feet can be affected. The tremor ranges from mild to severe and can interfere with daily functions. Although a resting tremor resolves with movement, reemergence of the tremor when movement is halted (e.g., when a hand holding a soup spoon stops to deliver food to the mouth) can be debilitating. The classic parkinsonian "pill-rolling" tremor, a finger tremor in which the thumb and fingers move as if rolling a pill back and forth, is considered uncommon in DIP. However, because a pill-rolling tremor may occur intermittently in DIP, its absence on exam is not a firm basis for distinguishing Parkinson's disease from DIP (Shuaib *et al.* 2016). *Rabbit syndrome*, a variant of DIP, is characterized by a rapid tremor of the lips and perioral area that resembles the rapid chewing-type movements of a rabbit's mouth (Villeneuve 1972).

The time course for developing DIP varies, but time of onset after drug exposure is usually later than for acute drug-induced akathisia or dystonia (Ayd 1961). For this reason, diagnosis of DIP is typically supported by a subacute onset over the days to weeks after starting the offending drug or increasing its dosage, or after reducing the dosage of an antiparkinsonian medication used to treat DIP or acute drug-induced dystonia. This temporal relationship between medication initiation and motor symptom onset should be evident, along with absence of symptoms prior to initiation of treatment with the drug and resolution of symptoms within 6 months after drug discontinuation (Wisidagama *et al.* 2021). Drug dosage influences the timing of DIP onset (Levinson *et al.* 1990), and overall risk varies across the antipsychotics and other agents causing DIP. Most antipsychotic (or anti-dopaminergic) DIP emerges in 1-3 weeks, and 90% of cases are evident by 3 months (Ayd 1961; Freyhan 1959; Medina *et al.* 1962). DIP can also develop insidiously; for example, DIP secondary to calcium channel blockers may not arise until after 9-12 months of treatment (Bondon-Guitton *et al.* 2011; Llau *et al.* 1994; Thanvi and Treadwell 2009).

Discontinuation of the causal agent is expected to result in resolution of DIP, but the clinical course may not be straightforward. Differentiating DIP from idiopathic Parkinson's disease is especially challenging in older individuals who have been maintained on long-term, stable medications that are known to cause DIP. At issue is whether the medication "unmasks" Parkinson's disease or whether older age renders a patient more sensitive to the medication's effects. In either case, stopping the medication reduces parkinsonism, although complete resolution of DIP may take more than a year. When underlying Parkinson's disease neuropathology is present, parkinsonism will eventually resume and progress. A Canadian autopsy series found that

DRB antipsychotics can unmask preclinical Parkinson's disease, as demonstrated by cases with insufficient substantia nigra degeneration to manifest Parkinson's disease clinically once the offending drug was removed (Shuaib *et al.* 2016). Of etiological interest, the autopsy series did not find neuropathological evidence for neurotoxicity or nigral degeneration secondary to the effects of DRB antipsychotics (Shuaib *et al.* 2016).

Given that management and prognosis of DIP and Parkinson's disease differ, dopamine transporter (DAT) single-photon emission computed tomography (SPECT) scanning can be used to distinguish DIP from Parkinson's disease. In antipsychotic-induced DIP, there is postsynaptic D_2 receptor blockade, and DAT-SPECT nigrostriatal binding is expected to be normal; in Parkinson's disease, presynaptic nigrostriatal dysfunction results in reduced DAT-SPECT binding (Tinazzi *et al.* 2014).

Risk Factors

Identification of discrete risk factors for DIP is confounded by individual variations in drug dosage and exposure duration that confer susceptibility. Both DRB agents and dopamine-depleting agents are known to cause DIP, whereas the mechanisms underlying DIP associated with calcium channel blockers, gastrointestinal prokinetics, antidepressants, and antiarrhythmics are not fully understood (Lopez-Sendon *et al.* 2013). High drug potency, higher dosages, and longer exposure are clear drug-related risk factors for DIP. Older age, female sex, dementia, severe psychiatric disease, brain damage, idiopathic Parkinson's disease, hypertension, HIV infection, and preexisting evidence for drug-induced movements are regarded as possible risk factors (Wisidagama *et al.* 2021).

Offending Medications

Both DRB and non-DRB medications (see Table 36-1) are associated with DIP. With the greater focus on DRB antipsychotics as causal in DIP, the potential role of non-DRB psychiatric medications--such as antiepileptics or mood stabilizers, calcium channel blockers, gastrointestinal prokinetics, and antiarrhthymics--can be overlooked. Notably, antiepileptic medications, used to treat primary psychiatric conditions, chronic pain, or seizures, are a significant cause of DIP and other drug-induced movement disorders, including in individuals with epilepsy (Zaccara *et al.* 2004; Zhou *et al.* 2022).

Both valproate and lithium are recognized independent causes of DIP in the absence of antipsychotic exposure. Although mechanisms of valproate-induced and lithium-induced DIP are not known, a recent review of patients undergoing DAT-SPECT scanning found that, after antipsychotics, valproate and lithium were the most suspected causative agents of DIP. The diagnosis of DIP was supported by normal DAT scans in 8 of 9 patients taking lithium and in 11 of 17 patients taking valproate and resolution of symptoms after drug cessation (Friedman 2020; Yomtoob *et al.* 2018).

The prevalence of valproate-induced DIP is typically reported as less than 10%, although reported estimates range from 1.4% to 75% (Brugger *et al.* 2016). Rates of nonparkinsonian tremor caused by valproate are higher (Armon *et al.* 1996). DIP can occur with exposure to lithium only, but risk may be greater in patients receiving both lithium and an antipsychotic (Ghadirian *et al.* 1996). Case reports and small series also describe DIP secondary to antidepressants, particularly SSRIs, although trazodone and tricyclic agents in psychiatric and nonpsychiatric settings are also implicated (Gerber and Lynd 1998; Leo 1996). Mechanisms for SSRI-induced DIP are also unclear. Potential causes include serotonergic inhibition of dopamine or the effects of other drugs combined with an SSRI.

Prevention

Management of DIP starts with prevention. Clinical examination for evidence of parkinsonism and other abnormal movements should be conducted *before* starting any medication known to have this iatrogenic effect. This examination should be followed by efforts to use the lowest effective dosage of medication and to gradually raise the dosage with frequent monitoring for signs of parkinsonism in an ongoing manner, especially during the first 3 months of treatment. The Simpson-Angus Scale (SAS) is a standardized tool that is commonly used to evaluate DIP in clinical trials, despite the fact that only 7 of its 9 items assess rigidity signs and none assess tremor, bradykinesia, or postural instability (Friedman *et al.* 2005; Simpson *et al.* 1964). When the SAS is used to monitor DIP, the additional signs and their functional impact warrant initial and serial assessment, especially in older individuals or those with other risk factors for DIP (e.g., brain injury, drug-drug interactions). Systematic monitoring is also important because of the subacute nature of DIP, the variability in its onset, and the possibility that DIP signs may resolve spontaneously while the patient is still taking the offending antipsychotic (Marsden and Jenner 1980).

Treatment

Once DIP emerges and is symptomatic, initial management is to reduce the offending agent to the lowest clinically effective dosage and continue to monitor parkinsonian symptoms and signs for at least 6 months. At lower medication dosages, milder symptoms of DIP may not require any interventions. When possible, the offending drug should be stopped, although it may not be possible to discontinue medications without worsening psychiatric symptoms. Transition to a medication with a lower propensity for DIP is then indicated. Among antipsychotics, transition may involve switching or cross-titrating from an FGA to an SGA. Quetiapine and clozapine are the only commonly available SGAs that do not worsen parkinsonism. Pimavanserin, a selective inverse agonist at 5-HT_{2A} indicated for psychosis in Parkinson's disease, also does not cause parkinsonism. Currently, its use is restricted to patients with Parkinson's disease. When those medications are not feasible, an antipsychotic with increased anticholinergic effects, such as chlorpromazine or olanzapine, can be used.

When antipsychotic treatment is initiated with risks of DIP (plus acute motor side effects) in mind, many patients will not require adjunctive antiparkinsonian medications to manage DIP. The practice of prescribing antiparkinsonian medications, usually anticholinergics, to prevent effects of DIP on medication adherence is discouraged, even in younger patients.

Even in acute psychiatric settings, use of higher starting dosages of antipsychotics that then require acute use of antiparkinsonian medications can be counterproductive. An alternative strategy (Miller 1997) is to titrate the antipsychotic dosage to the "neuroleptic threshold" (i.e., the point of minimal hypokinesia or rigidity [Haase 1965]) and then use other medications, such as benzodiazepines, to manage agitation. During maintenance antipsychotic treatment, emergent DIP should be managed initially with attempts to reduce the antipsychotic dosage before adding an anticholinergic medication. Select situations (e.g., younger patients susceptible to acute dystonia) warrant additional monitoring and education before initiating antiparkinsonian therapy.

When dosage reductions or an alternate medication fails to resolve DIP or these strategies are not feasible, antiparkinsonian medications used to treat idiopathic Parkinson's disease are also used for DIP. Research on their efficacy is limited, as is research on their reported effects on DIP (Friedman 2014). For anticholinergics and amantadine, efficacy data are similar, but amantadine has a safer adverse-effect profile and, anecdotally, is recommended by movement disorder specialists for initial use (Fann and Lake 1976; Magnus 1980; Mamo *et al.* 1999). Yet, current prescribing practices remain influenced by the early open-label observations suggesting effectiveness of anticholinergic agents for DIP (Medina *et al.* 1962; Rashkis and Smarr 1957). For this reason, anticholinergic agents--namely, trihexyphenidyl, benztropine, and diphenhydramine (an antihistamine with anticholinergic properties)--remain the mainstays of treatment for DIP. Their actual efficacy is thought to be overestimated, as subsequent controlled trials primarily compared different anticholinergics, did not include placebo arms, or showed limited evidence for their efficacy over placebo (Wisidagama *et al.* 2021). Symptomatic but inconsistent benefit was also reported with L-dopa (Hardie and Lees 1988). Selegiline, a selective and irreversible monoamine oxidase (MAO) type B inhibitor used to treat Parkinson's disease, has also been used for DIP (Gewirtz *et al.* 1993). A single trial of propranolol for DIP showed no benefit relative to placebo (Metzer *et al.* 1993).

Amantadine for DIP has been investigated more extensively compared with anticholinergic agents, the data demonstrating its efficacy are less conflicting, and its safety profile, while not benign, is better tolerated in the elderly (Friedman *et al.* 2005; Mamo *et al.* 1999). Most clinical trials reported amantadine as equal in efficacy to benztropine or biperiden (not currently available in the United States) for DIP (DiMascio *et al.* 1976; Fann and Lake 1976; Konig *et al.* 1996; Silver *et al.* 1995; Stenson *et al.* 1976). Some studies reported amantadine as more effective than benztropine (Merrick and Schmitt 1973) or effective for DIP that is refractory to benztropine (Gelenberg 1978). Other studies reported amantadine as inferior to benztropine (Kelly *et al.* 1974), no more effective than placebo (Mindham *et al.* 1972), or unable to reduce antipsychotic-induced movements when used to replace an anticholinergic agent (McEvoy *et al.* 1987). These varying results can be attributed to differing methodologies and patient populations.

Based on these studies, amantadine 100-300 mg/day is regarded as effective for DIP. In patients with Parkinson's disease, amantadine appears to lose efficacy after several weeks (Mawdsley *et al.* 1972; Schwab *et al.* 1972). Most study durations were short, and there are no studies reporting on long-term efficacy of amantadine for DIP. Notably, there are no data supporting use of amantadine prior to initiating an anticholinergic for DIP.

Benztropine 1-8 mg as a total daily dosage is used to treat DIP. The maximum therapeutic response occurs in 3-10 days and response may take longer with more severe DIP (Fann and Lake 1976; DiMascio *et al.* 1976). The anticholinergic dosage can be increased until DIP is alleviated or the degree of anticholinergic side effects is unacceptable. There is no substantive difference in the reported efficacy of benztropine versus trihexyphenidyl.

When DIP remains uncontrolled on benztropine, a common practice is to add amantadine or substitute it as a single agent. A next step is often the addition of a benzodiazepine or a b-blocker, although there are few data to support either as a treatment. With severe DIP, a risk factor for NMS

(Levinson and Simpson 1986), the antipsychotic should be stopped temporarily.

Diphenhydramine is used to treat parkinsonism, including DIP in the elderly and mild cases of parkinsonism in other age groups. It is less effective than anticholinergics and carries risks for adverse effects (sedation, confusion) that affect older patients, but may be better tolerated in patients bothered by anticholinergic side effects. Diphenhydramine tends to be more sedating than anticholinergics, which may benefit some patients. Dosages generally range from 50 to 400 mg/day, given in divided doses.

Data supporting use of levodopa or dopamine agonists for DIP are limited. Usually, they are ineffective for DIP and may worsen psychosis or cause confusion (Friedman *et al.* 2005). For this reason, levodopa is not recommended as a treatment for typical DIP, although there may be specific instances in which a trial is indicated (e.g., severe, disabling DIP in younger individuals). Studies evaluating valproate or lithium DIP indicate occasional benefits from levodopa or dopaminergic drugs (Factor *et al.* 2019; Zhou *et al.* 2022). An analysis of Canadian health care data showed increased rates of dopaminergic drug prescribing among more than 1,700 patients age 65 years and older on lithium monotherapy, as compared to patients on antidepressants, suggesting that DIP is underrecognized and subject to a prescribing cascade associated with diagnosis of idiopathic Parkinson's disease (Marras *et al.* 2016).

Electroconvulsive therapy (ECT) is recognized as an effective treatment for both depression and motor symptoms in Parkinson's disease (Borisovskaya *et al.* 2016). Case reports describe similar benefits for DIP in patients receiving ECT for other psychiatric indications, but randomized clinical trials have not been conducted (Baez and Avery 2011; Goswami *et al.* 1989; Mukherjee and Debsikdar 1994; Sadananda *et al.* 2013). For individuals with depression or psychosis and DIP that cannot be managed with medication adjustments or adjunctive medications, ECT may be an effective option (Wisidagama *et al.* 2021).

Anticholinergic Prophylaxis Against Drug-Induced Parkinsonism

The controversy over anticholinergic prophylaxis stems from prospective and retrospective studies showing reduced rates of antipsychotic DIP when anticholinergics were prescribed prophylactically, but also showing that DIP developed in prophylactically treated patients (Friedman 2014; Friedman *et al.* 2005; Mamo *et al.* 1999). Further concerns are data showing that anticholinergics reduced the effects of antipsychotics on positive symptoms (Johnstone *et al.* 1983) and increased the risk of TD (Hyde *et al.* 2005). Accordingly, routine prescription of anticholinergic medications to counter potential DIP in patients receiving antipsychotics is not recommended, nor is indefinite use of such medications once they are prescribed (Friedman 2014; Mamo *et al.* 1999; World Health Organization 1990). Use of anticholinergic medications is contraindicated in elderly individuals, because the risks carried by these agents--memory loss, confusion, blurred vision, urinary retention, glaucoma exacerbation, and dry mouth--are greater than their potential benefits. For selected patients, especially younger individuals, the risk-benefit assessment may warrant anticholinergic prophylaxis, but generally anticholinergics are used only after parkinsonism is known to have developed and other measures (dosage reduction and switching to an alternative medication) have been ineffective. Once stable status on an antipsychotic medication is achieved, slow withdrawal of the anticholinergic medication should be attempted. The slow taper avoids an acute anticholinergic withdrawal syndrome and chronic, indefinite anticholinergic use in the absence of actual benefits.

Tardive Dyskinesia and Tardive Syndromes

In addition to ascertaining whether there has been any DRB medication exposure, awareness of tardive syndrome nosology is important for accurate diagnosis and treatment planning; individuals can have more than one tardive subtype superimposed on nontardive movement disorders. Treatment approaches and prognoses differ for each movement disorder subtype, and accurate diagnosis of tardive versus nontardive DRB medication-induced movement disorders is especially critical. Notably, discontinuation or dosage reduction of the offending DRB medication causes a tardive syndrome to emerge, persist, or worsen, but causes a nontardive DRB medication-induced movement disorder to improve or resolve.

Facial dyskinesias that developed with prolonged treatment and that persisted after drug cessation were reported soon after chlorpromazine was introduced (e.g., Schonecker 1957). Because the movements appeared to develop after long-term (> 3 months) FGA treatment, the term *tardive dyskinesia* was coined to describe the persistent OBL dyskinetic movements (Faurbye *et al.* 1964). Given that the persistence of the movements, and not the timing of their onset, is the consistent feature of all tardive syndromes, the descriptive term *tardive*, a French word meaning "delayed" or "late," is a misnomer. Similar to misuse of the term *extrapyramidal* to describe *any* DRB drug-induced movement disorder (Hauser *et al.* 2022; Obeso 2019), use of the term *tardive dyskinesia* to refer to *all* persistent DRB drug-induced motor phenomena likewise causes confusion (Frei *et al.* 2018). For tardive syndromes, use of accurate terminology (e.g., tardive dystonia, tardive akathisia) to describe the observed phenomena is important because the treatment approaches used for the various tardive syndromes differ from the approaches used for the OBL movements of classic TD.

Whereas the general term *dyskinesia* is used to refer to any abnormal involuntary movement, *tardive dyskinesia* (i.e., "classic TD") is the diagnostic term used specifically to denote persistent, involuntary, and stereotyped OBL athetoid or choreiform movements that develop in association with exposure to DRB medications. Most often, antipsychotic drugs (with the possible exception of clozapine) are the responsible agents, but nonpsychiatric medications with DRB properties, such as antiemetics, can also cause TD. Dopamine-depleting drugs have not been shown to cause TD. Movements that resemble those of TD and appear to be caused by medications without DRB properties or by various medical conditions are, by definition, not classified as tardive disorders (D'Abreu and Friedman 2018; Frei *et al.* 2018). In that literature, mostly case reports, medications such as SSRIs or TCAs appear to unmask or exacerbate TD induced by earlier or concurrent use of DRB medications.

Tardive syndrome is the general term comprising persistent, iatrogenic hyperkinetic, hypokinetic, and sensory phenomena that can result from long-term exposure to DRB medications (Frei *et al.* 2018). The various tardive syndromes, classified according to their prevailing phenomena, include classic TD, tardive dystonia, tardive akathisia, tardive tics ("Tourettism"), tardive tremor, tardive myoclonus, and tardive pain and other sensory symptoms (Frei *et al.* 2018). The existence of tardive parkinsonism is under debate, as it may represent an unmasked underlying parkinsonian disorder. In addition to being socially disfiguring, the movements can cause embarrassment and impair function (Savitt and Jankovic 2018).

Although less common than classic TD, *tardive dystonia* is often more disabling. The concurrent presence of classic TD signs and a temporal relationship to DRB agents is useful in distinguishing tardive dystonia from idiopathic dystonia. Tardive dystonia tends to affect the limbs, neck, trunk, or face. Typically, the presentation is a focal dystonia involving neck and face muscles and manifesting as torticollis, retrocollis, or anterocollis, blepharospasm, jaw opening or trismus, grimacing, tongue protrusion, dysphagia, or respiratory stridor accompanied by distress or anxiety (Hauser *et al.* 2022). Sustained dystonia can result in unusual postures (e.g., truncal dystonia with opisthotonic posturing or arm extension and pronation with wrist flexion and internal rotation of the shoulders).

In comparison with classic TD, which is more common in women older than 60 years and tends to occur after lengthy exposure to DRB medication, tardive dystonia is more common in men younger than 40 years and tends to occur sooner after medication exposure. Most older patients will have a focal onset that progresses to segmental dystonia. Younger patients are more likely to present with generalized dystonia. Full remission is more likely in children and less likely in adults (Factor *et al.* 2019).

Tardive akathisia is usually accompanied by other tardive movements. It can persist for up to 7 years after DRB medications are discontinued and is typically resistant to pharmacological treatment (Frei *et al.* 2018). Tardive akathisia resembles acute akathisia in that there is subjective restlessness and tension with objective semi-purposeful or purposeless patterned motor movements (e.g., marching in place, repetitive self-touching, or crossing and uncrossing of legs). Acute akathisia occurs soon after DRB medication exposure, while tardive akathisia usually occurs later and persists or worsens after withdrawal of the offending drug. The presence of other tardive movements facilitates its diagnosis.

Rare tardive variants include DRB drug-induced tics, myoclonus, tremor, and sensory syndromes. Tardive tics, or tardive Tourettism, manifest as motor or vocal tics. Unlike Tourette syndrome, tardive tics have an older age at onset and occur after DRB medication exposure, but the phenomena are otherwise comparable. Tardive myoclonus is rare and is usually evident when the hands are held in certain postures. Tardive tremor tends to be a postural and kinetic tremor rather than a resting tremor. Tardive sensory syndromes can include an urge to move, paresthesias, and pain, or may present as a chronic oral or genital sensation (Frei *et al.* 2018).

Epidemiology

Tardive syndromes are common, affecting an estimated 20%-40% of patients on antipsychotic treatment, despite reduced reporting of TD after the introduction of SGAs and their promise of reduced motor side effects (Martino and Morgante 2017). In a meta-analysis of 41 randomized controlled trials (RCTs) that used FGAs and SGAs for psychotic disorders and were conducted from 2000 to 2015, prevalence of tardive syndromes was 30% among individuals treated with FGAs and 21% among those treated

with SGAs ($P = 0.002$) (Carbon *et al.* 2017). When patients with any FGA exposure were excluded, prevalence in the SGA group declined to 7%. Annual incidence of tardive syndromes in a meta-analysis of 57 RCTs was 6.5% (95% CI = 5.3%-7.8%) for FGAs and 2.6% (95% CI = 2.0%-3.1%) for SGAs (Carbon *et al.* 2018). Whereas SGAs confer a lower overall risk, the prospect of lower prevalence is offset by higher SGA prescribing rates, including off-label uses, a cumulative increased incidence of TD with ongoing antipsychotic use, and the usually irreversible nature of TD (Savitt and Jankovic 2018). Contributing to these rates is the noteworthy threefold increase in antipsychotic prescriptions between 1997 and 2011 in the United States (Friedman 2012). Risk factors for development of TD, aside from DRB medication exposure, include older age, female sex, diabetes mellitus, history of movement or cognitive disorder, intellectual developmental disorder or brain injury, history of DIP or acute DRB drug-induced movement disorder, longer duration of antipsychotic treatment, higher antipsychotic dosage, and family history of TD (Jankelowitz 2013). Commonly, the patient with classic TD is a woman age 60 years or older.

Presentation

Systematic assessments provide a basis for identifying tardive phenomena and monitoring their distribution, severity, and response to treatment (Hauser *et al.* 2022). Behavior and motor abnormalities associated with psychiatric illness, older age, and other drug-induced movements can confound assessment. Although not specifically designed to detect TD, several assessment tools are available that can facilitate baseline screening and longitudinal follow-up of classic TD. Examples are the Abnormal Involuntary Movement Scale (AIMS; Guy 1976; Munetz and Benjamin 1988) and the Dyskinesia Identification System: Condensed User Scale (DISCUS; Kalachnik and Sprague 1993). The Extrapyramidal Symptom Rating Scale (ESRS), a validated tool comparable to the AIMS for assessing classic TD, assesses other drug-induced movement disorders (parkinsonism, akathisia, and dystonia) and discriminates them from clinical psychiatric features (Chouinard and Margolese 2005). The ESRS can be useful since some patients have several DRB medication-induced movement disorders (e.g., elderly individuals are at greater risk for TD and DIP).

In classic TD, movements are hyperkinetic, complex, stereotyped, and rhythmic OBL and chewing movements such as lip smacking, puckering, pursing, sucking, mouth opening and closing, and tongue protrusion (see Hauser *et al.* 2022 for video examples). OBL and similar patterned movements in TD are referred to as *tardive stereotypies*--defined as repetitive, rhythmic, predictable, and often complex patterns of semi-purposeful or purposeless movements that resemble the normal range of movements for that body part, such as gestures or mannerisms. The earliest sign of TD may be a subtle worm-like movement of the tongue inside the mouth. This may evolve to broader side-to-side tongue movements followed by tongue curling, rolling, or twisting or pressing the tongue against the cheek ("bon-bon sign"). "Fly-catcher's tongue" sign refers to brief or prolonged involuntary tongue protrusion. Affected facial muscles cause blinking and blepharospasm. Patients can often suppress the movements voluntarily, such as when asked, while speaking, while eating, or by placing a finger on the lip. When the patient is distracted, the movements tend to increase. More severe TD affects speaking, eating, chewing, and swallowing and can cause oral ulcerations, dental complications, or jaw misalignment.

OBL stereotypies are often accompanied by corresponding repetitive, stereotyped movements of the hands and feet, such as piano-playing movements, hand-rubbing, pelvic thrusting, truncal rocking, foot tapping, or oscillations. Movements of the trunk and neck, however, tend to be irregular and unpredictable choreiform movements. Respiratory dyskinesias affecting the diaphragmatic and intercostal muscles cause irregular respiratory patterns or grunting and may predispose to aspiration. Severe esophageal or respiratory dyskinesias can be life threatening.

Clinical Course

Tardive syndromes usually emerge insidiously after months to years of treatment with a DRB agent or after its discontinuation. There are reports of tardive syndromes developing after brief exposures of several hours or days, but it is rare for tardive movements to begin within the first 3 months of DRB medication treatment. By definition, tardive phenomena require persistent abnormal movements for at least 1 month after stopping the DRB agent. Often, abnormal movements become apparent (i.e., are "unmasked") when the dosage of the offending DRB medication is reduced. Movements that resolve within 1 month of discontinuing the DRB agent can be attributed to acute or subacute DRB drug-induced conditions such as acute dystonia, acute akathisia, DIP, or NMS (Savitt and Jankovic 2018).

After initial symptom onset, the full tardive syndrome evolves over several days to weeks. Severity is highly variable, ranging from mild to severe, but the syndrome can stabilize to a chronic course that sometimes waxes and wanes. Most tardive syndromes persist and are permanent. Remission is reported in fewer than 25% of cases, but symptoms tend to improve over time and after DRB agents are discontinued (Gardos *et al.* 1988). DRB medication withdrawal, especially when abrupt, increases the dyskinesias, referred to as a withdrawal-emergent syndrome that can be avoided by gradual dosage reductions. Increasing the DRB medication dosage, and presumably dopamine blockade, reduces symptoms, a phenomenon referred to as "masked TD" (Savitt and Jankovic 2018).

The presence of multiple tardive disorders or nontardive drug-induced movements in the same patient adds to treatment complexity because treatments for tardive and nontardive syndromes have opposite effects. When there is evidence for a tardive syndrome, a first step is to determine whether acute or subacute DRB drug-induced movement disorders are also present. A tardive syndrome will persist or transiently worsen after dosage reduction or discontinuation of the DRB agent or after the addition of anticholinergic medications, whereas acute dystonia, acute akathisia, and DIP will improve. Managing concurrent tardive dystonia and classic TD is also challenging because their treatments counteract one another. When both are present, the predominant movement abnormality should be addressed.

Prevention

When clinical conditions require long-term treatment with DRB agents, the first arm of treatment is prevention. General caveats are to ensure clear indications for a medication and its duration, preferential use of agents with low risk of inducing TD, use of the lowest clinically effective dosage, minimized use of anticholinergic medications, and scheduled regular evaluations to review indications for the prescribed medication and to screen for signs of TD (and other drug-induced movements). Since patients can lack awareness of their abnormal movements or may not report them, visual observation of patients before and after starting DRB agents and documentation of findings should be a standard practice, including when clinical care is provided virtually. Additional caution and monitoring should be used in individuals with multiple TD risk factors.

Treatment

Initial management requires documentation of the type of phenomena, their severity, and their location or distribution, as well as follow-up diagnostic tests and neurological consultation as indicated; a review of treatment options with the patient and caregivers; and serial follow-up. When evidence supports diagnosis of a tardive syndrome, the first step, if tolerated by the patient, is gradual reduction and withdrawal of the offending agent.

Anticholinergic and antiparkinsonian medications should be discontinued. Anticholinergic agents may exacerbate TD and should not be used to treat TD. When there is significant parkinsonism or tardive dystonia, anticholinergic medications can be tapered gradually over 2 to 4 weeks with monitoring for side effects of anticholinergic cessation or worsening parkinsonism.

When long-term antipsychotic medications are needed, patients may be switched to a lower-potency agent such as quetiapine or clozapine, as these, among the SGAs, have the lowest risk of motor side effects. There are reports of clozapine-induced TD, although most studies support use of clozapine as an effective treatment for TD (Pardis *et al.* 2019). A small meta-analysis of four open-label trials ($n = 48$) (Mentzel *et al.* 2018) and a systematic review (Pardis *et al.* 2019) supported switching to clozapine monotherapy to reduce the risk for tardive movements or to treat a moderate to severe tardive syndrome.

Transient worsening of TD signs during withdrawal of DRB agents can be managed with low-dose benzodiazepines such as lorazepam or clonazepam if there is significant discomfort or anxiety (Bergman *et al.* 2018). If the movements become disabling and need to be suppressed, DRB agents are most effective but limit the prospects for remission.

Vesicular monoamine transporter 2 inhibitors. Development of the highly selective VMAT2 inhibitors valbenazine and deutetrabenazine and conduction of well-designed clinical trials yielded, in 2017, the first drugs specifically approved by the FDA to treat tardive syndrome. When initial management is inadequate, both are considered front-line interventions for TD, including when patients remain on DRB medications (Bhidayasiri *et al.* 2018). In treatment of tardive syndromes, VMAT2 inhibitors block transport of dopamine (and other monoamines) into vesicles at the synaptic cleft, resulting in reduced dopamine concentrations, reduced activation of postsynaptic dopamine receptors in the nigrostriatal pathway, and, consequently, decreased hyperkinetic movements. The main difference between the two drugs is the longer half-life of valbenazine, which is taken once daily at a dosage range of 40-80 mg/day, relative to deutetrabenazine, which is taken twice daily at a dosage range of 12-48 mg/day, must be taken with food, and has better tolerance overall.

Tetrabenazine, an older VMAT2 inhibitor, was approved for dyskinesias in Huntington's disease in 2008. Until the newer VMAT2 inhibitors became available, tetrabenazine

was also used off-label for TD. Its tolerability is influenced by its short half-life requiring three-times-daily dosing, fluctuating plasma levels, and development of somnolence or depression.

Safety concerns, tolerability, and cost are the primary barriers to use of VMAT2 inhibitors. Somnolence is a common side effect. All three VMAT2 inhibitors are metabolized in the liver by cytochrome P450 (CYP) 2D6 and raise concerns for QTc prolongation when prescribed with antipsychotics or CYP2D6 inhibitors, or taken by poor metabolizers. While addition of VMAT2 inhibitors improves TD, reductions in dopamine concentrations can aggravate parkinsonism, parkinsonian tremor, and other acute DRB medication-induced movement disorders to an intolerable degree.

For tardive dystonia or tardive akathisia, there is limited evidence as to whether VMAT2 inhibitors or adjustments in DRB medication dosage or type are beneficial, given that TD treatment trials have not distinguished which tardive subtypes were present. Tardive dystonia may benefit from anticholinergic agents such as benztropine or trihexyphenidyl, but these agents are relatively contraindicated in older patients. Clozapine can be especially beneficial for tardive dystonia when continued use of an antipsychotic is required.

Botulinum neurotoxin injections. Botulinum neurotoxin (BoNT) injections decrease presynaptic cholinergic release. BoNT type A (onabotulinumtoxin A) is approved to treat cranial and cervical dystonia, blepharospasm, and limb spasticity. As there are no RCTs on its use for TD, BoNT has a Level U recommendation (insufficient evidence) in the American Academy of Neurology (AAN) guideline for the treatment of TD (Bhidayasiri *et al.* 2018). Case reports and series and open-label reports suggest benefits of BoNT for TD in individuals with focal dystonia who have not responded to other interventions. While re-injections are required approximately every 3 months in perioral, lingual, or neck areas and have the potential to cause dysarthria and dysphagia, patient satisfaction with the procedure and its results is typically positive (Bashir and Jankovic 2020).

Other treatments. For patients who do not respond to VMAT2 inhibitors or experience intolerable adverse effects, the evidence base of treatment options is inconsistent. As mentioned above, a clozapine trial may be considered prior to or after use of VMAT2 inhibitors (Factor *et al.* 2019). Pathophysiological hypotheses of TD invoking oxidative stress or abnormalities of nondopaminergic neurotransmitters including GABA, glutamate, and acetylcholine have spawned studies on additional treatment approaches. Most of these studies were small and fraught with methodological limitations or nonreplication. However, as most of these medications are available for other indications, *n*-of-1 trials represent an option for individuals who are otherwise treatment nonresponsive or unable to tolerate clozapine or VMAT2 inhibitors.

Amantadine, first reported to reduce TD symptoms in 1971 and often used to treat levodopa-induced dyskinesias, has been prescribed to treat TD in the face of conflicting evidence (Lin and Ondo 2018). Results from several small RCTs of placebo versus amantadine at dosages up to 400 mg/day suggest that amantadine may have short-term benefit for TD at higher dosages than those used for other indications (Level C evidence) (Bhidayasiri *et al.* 2013). Use of amantadine requires monitoring for anticholinergic side effects and the risk for psychosis and livedo reticularis.

Benzodiazepines are frequently used in the treatment of TD, especially in the context of distress or dystonia; evidence for reduced tardive movements is less clear, especially for choreoathetoid movements. In a double-blind RCT crossover trial in which 19 patients with tardive dyskinesia received placebo or clonazepam (in divided doses up to 4.5 mg/day) over a 4-week period (Thaker *et al.* 1987), dyskinesia ratings (Maryland Psychiatric Research Center Scale; Cassady *et al.* 1997) decreased by 37% in participants treated with clonazepam, versus by 2% in those treated with placebo. Because that study has not been replicated, the 2013 AAN guideline stated that clonazepam may be effective for short-term (< 3 months) treatment of TD (Bhidayasiri *et al.* 2013). Small open-label studies of diazepam, alprazolam, and placebo did not demonstrate clear evidence of benefit (Lin and Ondo 2018). Tolerance to benzodiazepines over time and adverse cognitive effects are substantial liabilities.

Several compounds with antioxidant properties have been evaluated for treatment of tardive syndromes. Ginkgo biloba extract (EGb-761) was studied in three RCTs followed by a meta-analysis that showed benefits in TD relative to placebo (Zheng *et al.* 2016). The AAN guideline granted a Level B recommendation to Ginkgo biloba for treatment of TD; however, additional confirmatory studies are needed (Bhidayasiri *et al.* 2018). Small studies on vitamin B_6 (pyridoxal 5'-phosphate) up to 400 mg/day in placebo-controlled RCTs showed reduced dyskinesia scores (Lerner *et al.* 2001, 2007), but there are no reported confirmatory studies.

A meta-analysis showed benefits of vitamin E over placebo in 15 studies (Artukoglu *et al.* 2020), whereas a Cochrane Review of 13 RCTs reported no evidence for benefits of vitamin E over placebo (Soares-Weiser *et al.* 2018). Various other cholinergic agents (e.g., physostigmine, donepezil, deanol, choline, lecithin, meclofenoxate, tacrine) have been evaluated in TD (Lin and Ondo 2018). Trials of cholinesterase inhibitors suggested that these are of limited benefit for TD (Tammenmaa *et al.* 2004). Case reports and open-label trials showed benefits from donepezil for TD, but placebo-controlled RCTs of donepezil (Ogunmefun *et al.* 2009) and of galantamine (Caroff *et al.* 2007) failed to find significant benefits over placebo. Two open-label studies of the branched-chain amino acids leucine, isoleucine, and valine suggested benefits for TD (Richardson *et al.* 1999, 2003), but there are no published follow-up data.

Unlike acute akathisia, tardive akathisia is unlikely to respond to b-blockers, anticholinergics, amantadine, or benzodiazepines.

Neurostimulation. ECT may be beneficial for TD, especially in older patients with concurrent DIP, or as per case reports, when ECT is used to treat depressive illnesses or schizophrenia in patients with concurrent TD (Weiner and Reti 2017). A retrospective case series of 18 patients with TD receiving ECT showed a 10-point improvement in the AIMS score (Yasui-Furukori *et al.* 2014). As other studies failed to show benefits or demonstrated worsening of TD after ECT, AAN guidelines indicate that there is insufficient evidence (Level U) for efficacy of ECT for treatment of TD (Bhidayasiri *et al.* 2013).

Deep brain stimulation (DBS) is used for severe and treatment-refractory TD, usually with tardive dystonia. Further research on efficacy and safety is needed, as most analyses relied on open-label case reports, garnering Level C evidence per AAN guidelines (Bhidayasiri *et al.* 2013). A meta-analysis of 117 patients with refractory tardive syndromes who underwent DBS, primarily targeting the bilateral posteroventral globus

pallidus pars interna, showed evidence for significant improvement on measures of classic TD and dystonia (Macerollo and Deuschl 2018). One RCT evaluated pallidal DBS versus sham treatment for tardive syndromes, including dystonia and dyskinesia (Gruber *et al.* 2018). Group differences in tardive symptom ratings were not statistically significant at 3 months (improvement was 22.8% for DBS vs. 12.0% for sham); at the end of a 6-month open-label extension phase, though, there was an overall improvement of 41.5% and any adverse effects associated with DBS resolved. In the one double-blind RCT of repetitive transcranial magnetic stimulation (rTMS) versus sham over the motor cortex for 10 days ($n = 26$), the active rTMS group had significantly reduced tardive symptoms (Khedr *et al.* 2019).

Summaries of Pharmacological Treatments

Anticholinergic Medications

Trihexyphenidyl

History and discovery. Trihexyphenidyl, a synthetic analog of atropine, was introduced as benzhexol hydrochloride in 1949. It was found to be effective in the treatment of Parkinson's disease in a study of 411 patients (Doshay *et al.* 1954). Thereafter, it was also used to treat antipsychotic-induced parkinsonism (Rashkis and Smarr 1957).

Structure-activity relations. Trihexyphenidyl, a tertiary-amine analog of atropine, is a competitive antagonist of acetylcholine and other muscarinic agonists that compete for a common binding site on muscarinic receptors (Yamamura and Snyder 1974). It exerts little blockade at nicotinic receptors (Timberlake *et al.* 1961). Trihexyphenidyl and all drugs in this class are referred to as anticholinergic, antimuscarinic, or atropine-like drugs. As a tertiary amine, trihexyphenidyl readily crosses the blood-brain barrier (Brown and Taylor 1996).

Pharmacological profile. The pharmacological properties of trihexyphenidyl resemble those of atropine and other anticholinergic drugs, although trihexyphenidyl acts primarily centrally, with few peripheral effects and little sedation. In the eye, anticholinergic drugs block both the sphincter muscle of the iris, causing the pupil to dilate (mydriasis), and the ciliary muscle of the lens, preventing accommodation and causing cycloplegia. In the heart, anticholinergic drugs usually produce a mild tachycardia through vagal blockade at the sinoatrial node pacemaker, although a mild slowing can occur. In the gastrointestinal tract, anticholinergic drugs reduce gut motility and salivary and gastric secretions. Salivary secretion is particularly sensitive and can be completely abolished. In the respiratory system, anticholinergic agents reduce secretions and can produce mild bronchodilatation. Anticholinergics inhibit the activity of sweat glands and mildly decrease contractions in the urinary and biliary tracts (Brown and Taylor 1996).

Pharmacokinetics and disposition. Peak concentration for trihexyphenidyl is reached 1-2 hours after oral administration, and its half-life is 10-12 hours (Cedarbaum and McDowell 1987). As a tertiary amine, trihexyphenidyl crosses the blood-brain barrier to enter the central nervous system (CNS).

Mechanism of action. The presumed mechanism of action of trihexyphenidyl for treatment of acute dystonic reactions or DIP is blockade of intrastriatal cholinergic activity. Compared with nigrostriatal dopaminergic activity, which is decreased by antipsychotic blockade, intrastriatal cholinergic activity is relatively increased. Blockade of cholinergic activity returns the system to its previous equilibrium.

Indications. Trihexyphenidyl, along with the other listed anticholinergics, has FDA approval for treatment of all forms of parkinsonism, including DIP. Trihexyphenidyl can be used to treat acute medication-induced dystonia. Much higher dosages (up to 75 mg/day) have been used for the treatment of primary dystonia. Trihexyphenidyl has limited utility for medication-induced akathisia, except when there is co-occurring DIP.

The benefits of anticholinergic medications are limited by their adverse effects on cognition and memory (Jabbari *et al.* 1989; Taylor *et al.* 1991). Side effects correlate with blood levels, but efficacy does not (Burke and Fahn 1985). The individual therapeutic dosage and duration of is determined empirically and varies widely.

Side effects and toxicology. The *peripheral* side effects of trihexyphenidyl result from its parasympathetic muscarinic blockade and occur in a consistent hierarchy among different organs. They are qualitatively similar to side effects of atropine and other anticholinergic drugs, but are quantitatively less because of the reduced peripheral activity of trihexyphenidyl (Brown 1990).

Anticholinergic drugs initially depress salivary and bronchial secretions and sweat production. Reduced salivation leads to dry mouth and contributes to the high incidence of dental caries found among patients with chronic psychiatric problems (Winer and Bahn 1967). Treatment for this condition is unsatisfactory; relief obtained from chewing sugar-free gum or sucking on hard candy is limited by the need for constant use. Reduced sweating can contribute to heat prostration and heatstroke, particularly in warmer ambient temperatures.

The next physiological effects occur in the eyes and heart. Pupillary dilatation and inhibition of accommodation in the eye lead to photophobia and blurred vision. Attacks of acute glaucoma can occur in susceptible individuals with narrow-angle glaucoma, although this is relatively uncommon. Vagus nerve blockade leads to increased heart rate and is more apparent in patients with high vagal tone (usually younger men).

The next effects are inhibition of urinary bladder function and bowel motility, which can produce urinary retention, constipation, and obstipation. Sufficiently high dosages of anticholinergics will inhibit gastric secretion and motility (Brown and Taylor 1996).

Memory disturbance is the most common *central* side effect of anticholinergic medications because memory is dependent on the cholinergic system (Drachman 1977). Patients with underlying brain pathology are more susceptible to memory disturbance (Fayen *et al.* 1988). Patients with chronic psychiatric conditions often have a decreased ability to express themselves, making evaluation of memory more difficult; therefore, subtle memory changes can be missed or attributed to the underlying illness.

Memory disturbances are aggravated in patients with Parkinson's disease treated with anticholinergics (Yahr and Duvoisin 1968), even in some patients receiving only small dosages (Stephens 1967). For example, patients receiving an antipsychotic and benztropine had significantly increased overall scores on the Wechsler Memory Scale when benztropine was withdrawn (Baker *et al.* 1983).

Anticholinergic toxicity produces restlessness, irritability, disorientation, hallucinations, and delirium. Elderly patients are at increased risk for both memory loss and toxic delirium, even at very low dosages, because of the natural loss of cholinergic neurons with aging (Perry *et al.*

1977). Toxic dosages can produce a clinical situation identical to atropine poisoning, manifesting as fixed dilated pupils, flushed face, sinus tachycardia, urinary retention, dry mouth, and fever. This condition can proceed to coma, cardiorespiratory collapse, and death.

Drug-drug interactions. Anticholinergic effects, including side effects, may increase when trihexyphenidyl or any anticholinergic is combined with amantadine. Anticholinergic side effects are also more likely to occur when these agents are combined with other drugs with anticholinergic properties.

As to whether anticholinergic medications affect antipsychotic blood levels, the best studies indicate that anticholinergic drugs either do not affect antipsychotic blood levels, or, at most, lower these levels only transiently (McEvoy 1983).

Anticholinergic abuse. Anticholinergic drugs may be abused for their euphoriant and hallucinogenic effects, or combined with street drugs for enhanced effect (Crawshaw and Mullen 1984). The abuse potential of anticholinergic drugs in psychiatric and nonpsychiatric patients is attributed to their indirect effect as a dopamine agonist in the limbic system (Naja and Halaby 2017). Patients with a history of substance abuse have a greater potential to abuse anticholinergics. However, in some individuals with schizophrenia who used higher-than-prescribed dosages, reports of "abuse" were associated with reduced antipsychotic-induced anhedonia, improved function, and minimal, if any, adverse anticholinergic effects (Wells *et al.* 1989). Cases of abuse are reported with all anticholinergics, but trihexyphenidyl is the drug for which abuse is most frequently reported, followed by benztropine (Chiappini *et al.* 2022). It is unclear whether the higher reported rates of abuse of these agents is related to their unique properties versus their greater general availability relative to other anticholinergic medications.

Benztropine

History and discovery. Benztropine was synthesized by uniting the tropine portion of atropine with the benzhydryl portion of diphenhydramine hydrochloride. Benztropine was found to be effective in the treatment of

302 patients with Parkinson's disease (Doshay 1956). The best results in the control of rigidity, contracture, and tremor were obtained at benztropine dosages of 1-4 mg once daily for older patients and 2-8 mg once daily for younger ones. Dosages of 15-30 mg once daily caused excessive flaccidity in some patients, who became unable to lift their arms or raise their heads off the bed. Subsequently, benztropine was found to be effective for treatment of DIP (Karn and Kasper 1959).

Structure-activity relations. Benztropine is a tertiary amine with activity similar to that of trihexyphenidyl. As a tertiary amine, benztropine enters the CNS.

Pharmacological profile. Benztropine has the pharmacological properties of an anticholinergic and an antihistaminic; however, it produces less sedation (in experimental animals) than diphenhydramine.

Pharmacokinetics and disposition. Little is known about the pharmacokinetics of benztropine. A correlation between serum anticholinergic levels and the presence of DIP is documented (Tune and Coyle 1980). There is little correlation between the total daily dosage of benztropine and the serum anticholinergic level, with the serum activity for a given dosage varying 100-fold between subjects. When treated with higher dosages of anticholinergics, patients with DIP show increased serum anticholinergic activity and decreased abnormal movements. Relatively small increases in the oral dosage of an anticholinergic drug can result in significant nonlinear increases in serum anticholinergic activity levels. Benztropine has a long-acting effect and can be given once or twice a day.

Mechanism of action, side effects, and drug-drug interactions.

The mechanism of action and the drug interactions for benztropine are similar to those of trihexyphenidyl. The side effects of these two drugs are also similar, but the degree of sedation produced by benztropine may be less (Doshay 1956).

Indications. Benztropine, like the other listed anticholinergics, has FDA approval for use in the treatment of all forms of parkinsonism, including

DIP. Intramuscular benztropine is a first-line treatment for acute dystonic reactions.

Biperiden

Biperiden, not currently available in the United States, is an analog of trihexyphenidyl that has greater peripheral anticholinergic activity than trihexyphenidyl and greater activity against nicotinic receptors (Timberlake *et al.* 1961). Biperiden is well absorbed from the gastrointestinal tract. Its metabolism, while not completely understood, involves liver hydroxylation. Its activity, pharmacological profile, and side effects resemble those of other anticholinergics. It is indicated for treatment of DIP.

Procyclidine

Procyclidine is an analog of trihexyphenidyl (Schwab and Chafetz 1955). Its activity, pharmacology, and side effects resemble those of other anticholinergics. It is indicated for treatment of DIP. The limited pharmacokinetic data show that it is rapidly absorbed, with a 12-hour half-life after oral or intravenous administration, extensive metabolism in the liver, and a relatively low urine clearance rate. Accordingly, dosage adjustments are indicated in older persons or in individuals with hepatic dysfunction (Whiteman *et al.* 1985).

Antihistaminic Medications

Diphenhydramine

History and discovery. Antihistaminic agents have been used for the treatment of Parkinson's disease. Diphenhydramine, one of the first antihistamines developed and used clinically (Bovet 1950), was the primary antihistamine studied in treatment of DIP. Although some antihistamines may be effective, other antihistamines have not been studied systematically for treatment of DIP.

Structure-activity relations. All drugs referred to as antihistamines are reversible competitive inhibitors of histamine at the histamine 1 (H_1)

receptor. Some antihistamines also inhibit the action of acetylcholine at the muscarinic receptor. It is believed that central muscarinic blockade, rather than histaminic blockade, is responsible for the therapeutic effect of antihistamines in DIP or acute dystonic reactions. Ethanolamine antihistamines (i.e., diphenhydramine, dimenhydrinate, and carbinoxamine maleate) have the greatest anticholinergic activity, and ethylenediamine antihistamines have the least anticholinergic activity. Antihistamines such as terfenadine and astemizole have no anticholinergic activity, whereas many of the remaining antihistamines have very mild anticholinergic activity (Babe and Serafin 1996).

Pharmacological profile. Antihistamines inhibit the constrictor action of histamine on respiratory smooth muscle. They restrict the vasoconstrictor and vasodilatory effects of histamine on vascular smooth muscle and block histamine-induced capillary permeability. Antihistamines with CNS activity are depressants, producing diminished alertness, slowed reaction times, and somnolence. They can also block motion sickness. Antihistaminic drugs with anticholinergic activity also possess mild antimuscarinic pharmacological properties similar to those of other atropine-like drugs (Babe and Serafin 1996).

Pharmacokinetics and disposition. Diphenhydramine is well absorbed from the gastrointestinal tract. Peak concentrations occur 2-3 hours after oral administration. Its therapeutic effects usually last 4-6 hours, and it has a half-life of 3-9 hours. Diphenhydramine is widely distributed throughout the body, and as a tertiary amine, it enters the CNS. Age does not affect its pharmacokinetics. It undergoes demethylations in the liver and is then oxidized to carboxylic acid (Paton and Webster 1985).

Mechanism of action. Diphenhydramine possesses some anticholinergic activity, which is believed to be the basis for its effect in diminishing DIP and acute dystonic reactions.

Indications. Diphenhydramine has FDA approval for treatment of parkinsonism, including DIP, in the elderly and for mild cases of parkinsonism in other age groups. It is used as an oral or parenteral agent to treat acute dystonic reactions. There is no conclusive evidence that it is helpful for akathisia or nonparkinsonian tremor. Diphenhydramine also has indications for multiple other conditions that are not related to drug-induced movement disorders.

Side effects and toxicology. The primary side effect of diphenhydramine is sedation. Although other antihistamines may cause gastrointestinal distress, diphenhydramine has a low incidence of such an effect. Drying of the mouth and respiratory passages can occur. In general, the toxic effects are similar to those of trihexyphenidyl and of other anticholinergics.

Drug-drug interactions. Diphenhydramine has no reported interactions with other drugs, but it has an additive depressant effect when used in combination with alcohol or with other CNS depressants.

Dopaminergic Medications

Amantadine

History and discovery. Anticholinergic side effects and inadequate treatment response eventually led to the investigation of other agents to treat antipsychotic-induced movement disorders. Initially, both methylphenidate and intravenous caffeine

were investigated as treatments for DIP, but neither agent achieved general use, despite apparent efficacy (Brooks 1956; Freyhan 1959).

Amantadine is an antiviral agent that is effective against A2 (Asian) influenza (Wingfield *et al.* 1969). It was unexpectedly found to produce symptomatic improvement in patients with Parkinson's disease (Parkes *et al.* 1970; Schwab *et al.* 1969). Subsequently, it was reported as effective for DIP (Kelly and Abuzzahab 1971).

Structure-activity relations. Amantadine is a water-soluble tricyclic amine. It binds to the Matrix-2 (M2) protein, a membrane protein that functions as an ion channel on the influenza A virus (Hay 1992). Its activity in reducing DIP is not known. Earlier animal studies implicated direct and indirect effects on dopamine neurons. More recent studies demonstrated weak, noncompetitive *N*-methyl-D-aspartate antagonist effects with antiglutamatergic properties. Clinically, anticholinergic-like side effects are evident (e.g., dry mouth, urinary retention, constipation), despite the fact that the drug does not possess direct anticholinergic activity in animal studies, although it has been shown to have activity at glutamate receptors (Stoof *et al.* 1992).

Indications. Amantadine has FDA approval for the treatment and prophylaxis of influenza A respiratory illness and for the treatment of Parkinson's disease and secondary causes of parkinsonism, including DIP, postencephalitic parkinsonism, and parkinsonism associated with carbon monoxide intoxication or cerebral arteriosclerosis. Amantadine is commonly used in the management of levodopa-induced dyskinesias (Vijayakumar and Jankovic 2016). Amantadine has a Level C recommendation for the treatment of TD (Bhidayasiri *et al.* 2018) based on initial small case series and mixed results from two small RCTs (Angus *et al.* 1997; Pappa *et al.* 2010).

Limited data show that amantadine may benefit a small number of patients with akathisia, but there is insufficient evidence to recommend its use for that purpose.

Pharmacokinetics and disposition. In young healthy individuals, amantadine is slowly and well absorbed from the gastrointestinal tract, with unchanged oral bioavailability over a dosage range of 50-300 mg/day. It reaches steady state in 4-7 days. Plasma concentrations (0.12-1.12 mg/mL) may have some correlation with improvement in DIP (Greenblatt *et al.* 1977; Pacifici *et al.* 1976). Amantadine has relatively constant blood levels and a long duration of action (Aoki *et al.* 1979) and is excreted unchanged by the kidneys. Its elimination half-life is 16-17 hours and is more prolonged in elderly individuals and patients with impaired renal function (Hayden *et al.* 1985).

Mechanism of action. Amantadine inhibits viral replication by binding to the M2 protein on the viral membrane and inhibiting replication (Hay 1992). Its mechanism of action as an antiparkinsonian agent is less clear.

Amantadine has no anticholinergic activity in tests on animals, being only 1/209,000 as potent as atropine (Grelak *et al.* 1970). It appears to cause the release of dopamine and other catecholamines from intraneuronal storage sites via an amphetamine-like mechanism. It has also been shown to have activity at glutamate receptors, which may contribute to its antiparkinsonian effect (Stoof *et al.* 1992). Amantadine has preferential selectivity for central catecholamine neurons (Grelak *et al.* 1970; Stromberg *et al.* 1970).

Side effects and toxicology. At dosages of 100-300 mg/day, amantadine does not produce adverse effects as readily as do anticholinergic medications. Side effects of amantadine result from CNS stimulation. The most common reported side effects are nausea, dizziness (lightheadedness), and insomnia. Other side effects include irritability, tremor, dysarthria, ataxia, vertigo, agitation, reduced concentration, hallucinations, and delirium (Postma and Van Tilburg 1975). Hallucinations are often visual. Side effects are more likely to occur in elderly patients and in patients with reduced renal function (Borison 1979; Ing *et al.* 1979). Toxic effects are directly related to elevated amantadine serum levels (> 1.5 mg/mL). Resolution of toxic symptoms is dependent on renal clearance and may require dialysis in extreme cases, although less than 5% of amantadine is removed through dialysis.

Patients with congestive heart failure or peripheral edema should be monitored because of amantadine's ability to increase the availability of catecholamines. Long-term use of amantadine may produce livedo reticularis in the lower extremities from the local release of catecholamines and resulting vasoconstriction (Cedarbaum and Schleifer 1990). Amantadine should be used with caution in patients with seizures because of possible increased seizure activity. Amantadine is embryotoxic and teratogenic in animals, but there are no well-controlled studies in women regarding teratogenicity.

Drug-drug interactions. There are no reported interactions between amantadine and other drugs. There may be increased anticholinergic side effects when amantadine is used in combination with an anticholinergic agent.

Other precautions. Amantadine should not be discontinued abruptly, because this can result in an acute parkinsonian crisis or precipitate delirium, agitation, delusions, hallucinations, paranoia, stupor, anxiety, depression, or slurred speech. Cases of possible NMS have also been reported after dosage reductions or withdrawal of amantadine, warranting careful observation, especially in patients prescribed DRB agents, when the amantadine dosage is abruptly reduced or the drug is discontinued.

Amantadine dosages should be reduced in patients with renal impairment and in individuals age 65 years or older. Reduced dosages may also be required in the context of congestive heart failure, peripheral edema, or orthostatic hypotension.

Beta-Adrenergic Receptor Antagonists

History and Discovery

Propranolol was reported to be effective for the treatment of restless legs syndrome (Ekbom syndrome [Ekbom 1965]), which resembles the physical movements of akathisia (Strang 1967). Later it was reported to be effective in the treatment of medication-induced akathisia (Kulik and Wilbur 1983; Lipinski *et al.* 1983). Subsequently, other b-blockers have been investigated for the treatment of akathisia.

Structure-Activity Relations

Competitive b-adrenergic receptor antagonism is a property common to all b-blockers. b-Blockers are distinguished by the additional properties of their relative affinity for b_1 and b_2 receptors (selectivity), lipid solubility, intrinsic b-adrenergic receptor *agonist* activity, blockade of receptors, capacity to induce vasodilation, and general pharmacokinetic properties (Hoffman and Lefkowitz 1996). b-Blockers with high lipid solubility readily cross the blood-brain barrier.

Pharmacological Profile

The major pharmacological effects of b-blockers involve the cardiovascular system. b-Blockers slow the heart rate and decrease cardiac contractility; however, these effects are modest in a normal heart. In the lung, they can cause bronchospasm, although, again, there is little effect in normal lungs. They block glycogenolysis, preventing production of glucose during hypoglycemia (Hoffman and Lefkowitz 1996). b-Blockers affect lipid metabolism by preventing release of free fatty acids while elevating triglycerides (Miller 1987). In the CNS, they produce fatigue, sleep disturbance (insomnia and nightmares), and CNS depression (see Drayer 1987; Gengo *et al.* 1987).

All b-blockers, except atenolol and nadolol, are well absorbed from the gastrointestinal tract (McDevitt 1987). All b-blockers undergo metabolism in the liver. Propranolol and metoprolol undergo significant first-pass effects, with bioavailability as low as 25%. Large interindividual variation (as much as 20-fold) leads to wide variation in clinically therapeutic dosages (Hoffman and Lefkowitz 1996). Metabolites appear to have limited b-receptor antagonistic activity. The degree to which a particular b-blocker enters the CNS is related directly to its lipid solubility.

Mechanism of Action

The exact mechanism of action of b-blockers in the treatment of drug-induced abnormal movements is unclear. The existence of a noradrenergic pathway from the locus coeruleus to the limbic system has been proposed as a modulator involved in symptoms of TD, akathisia, and tremor (Wilbur *et al.* 1988). It appears that lipid solubility and the corresponding ability to enter the CNS are the most important factors determining the efficacy of a b-blocker in treating akathisia and perhaps other types of drug-induced abnormal movements (Adler *et al.* 1991).

Indications

b-Blockers have FDA approval primarily for cardiovascular indications, and propranolol is also indicated for familial essential tremor, but there are no

FDA-approved indications for the treatment of any type of medication-induced movement disorders.

b-Blockers are considered to be the first-line treatment for akathisia. In addition to their indication for essential tremor, b-blockers have been reported to be beneficial for tremor in Parkinson's disease (Foster *et al.* 1984) and for lithium-induced tremor (Gelenberg and Jefferson 1995), but not for antipsychotic-induced tremor (Metzer *et al.* 1993).

Side Effects and Toxicology

The side effects of b-blockers result from b-receptor blockade. b_2-Blockade of bronchial smooth muscle produces bronchospasm. Individuals with normal lung function are unlikely to be affected, but smokers and others with lung disease can develop serious breathing difficulties. b-Blockers can contribute to heart failure in susceptible individuals, such as those with compensated heart failure, acute myocardial infarction, or cardiomegaly. Abrupt cessation of b-blockers can also exacerbate coronary heart disease in susceptible patients, producing angina or, potentially, myocardial infarction (for details, see Hoffman and Lefkowitz 1996).

In individuals with normal heart function, bradycardia produced by b-blockers is insignificant; however, in patients with conduction defects or when combined with

other drugs that impair cardiac conduction, b-blockers can contribute to serious conduction problems.

b-Blockers can block the tachycardia associated with hypoglycemia, eliminating this warning sign in patients with diabetes. b_2 blockade also can inhibit glycogenolysis and glucose mobilization, interfering with recovery from hypoglycemia (Hoffman and Lefkowitz 1996).

b-Blockers can impair exercise performance and produce fatigue, insomnia, and major depressive disorder. However, the development of major depressive disorder probably only occurs in individuals predisposed to developing an affective disorder.

Drug-Drug Interactions

b-Blockers can have significant interactions with other drugs. Chlorpromazine in combination with propranolol may increase the blood levels of both drugs. Additive effects on cardiac conduction and blood pressure can occur when b-blockers are combined with drugs having similar effects (e.g., calcium channel blockers). Phenytoin, phenobarbital, and rifampin increase the clearance of propranolol. Cimetidine increases propranolol blood levels by decreasing hepatic metabolism. Theophylline clearance is reduced by propranolol. Aluminum salts (antacids), cholestyramine, and colestipol may reduce the absorption of b-blockers (Hoffman and Lefkowitz 1996).

Benzodiazepines

History and Discovery

Diazepam was first shown to be effective in the treatment of restless legs syndrome (Ekbom syndrome), which resembles the physical movements of akathisia (Ekbom 1965). Subsequently, diazepam, lorazepam, and clonazepam were reported to be beneficial for medication-induced akathisia (Adler *et al.* 1985; Donlon 1973; Kutcher *et al.* 1987). Clonazepam was reported to be beneficial for drug-induced dystonia (O'Flanagan 1975) and TD (Thaker *et al.* 1987).

Mechanism of Action

All benzodiazepines promote binding of GABA to $GABA_A$ receptors, magnifying the effects of GABA. The mechanism by which these agents improve antipsychotic-induced movement disorders is unknown, but it may be related to their augmentation of the inhibitory GABAergic effect (Hobbs *et al.* 1996). The properties of benzodiazepines are discussed in detail in Chapter 22.

Indications

Benzodiazepines have FDA approval for use in treatment of anxiety disorders, agoraphobia, insomnia, and seizure disorders; management of alcohol withdrawal; anesthetic premedication; and skeletal muscle relaxation. Although benzodiazepines are not approved to treat any specific medication-induced movement disorders, they are sometimes used to reduce anxiety, distress, or agitation associated with an acute drug-induced movement disorder.

Lorazepam and clonazepam are the two primary benzodiazepines studied in the treatment of drug-induced movement disorders. Clonazepam has a long duration of action and can be given once a day. Lorazepam (intermediate-acting) has the advantage of possessing no active metabolites, which limits its potential side effects and toxicity. Short-term benzodiazepine use can have some utility for drug-induced movement disorders when there is significant distress or agitation. Otherwise, the risks of diversion, falls, and cognitive effects with any duration of use are compounded by the development of tolerance and risks of dependence and withdrawal with longer-term benzodiazepine use (Pringsheim *et al.* 2018).

In the remote past, clonazepam was reported as effective in the treatment of TD (Bobruff *et al.* 1981; Thaker *et al.* 1990). Dosages of 1-10 mg/day were used in the first study (Bobruff *et al.* 1981), although the optimal dosage was found to be 4 mg/day, with many patients unable to tolerate higher dosages. The second study used dosages of 2-4.5 mg/day, and tolerance developed after 5-8 months (Thaker *et al.* 1990). Other studies were limited by short durations and small sample sizes, with subjects also receiving antiparkinsonian agents.

A relatively recent systematic review (Bergman *et al.* 2018) on the effectiveness of benzodiazepines as adjunctive treatment for TD identified four small RCTs, comprising a total of 75 individuals with antipsychotic-induced TD. The absence of differences between treatment groups in the improvement in TD features and the low quality of the evidence led the authors to conclude that benzodiazepines are not indicated for routine clinical use and that any use should be considered experimental, and warrants caution, given the risk for adverse effects (Bergman *et al.* 2018).

A systematic review examining the treatment of antipsychotic-induced akathisia reported on two small RCTs of 7-14 days' duration comparing clonazepam with placebo across a total of 27 participants (Pringsheim *et al.* 2018). In both studies, clonazepam was significantly beneficial and well-tolerated, supporting its use as an option for short-term treatment, starting at a dosage of 0.5 mg/day, with slow titration to the lowest effective dosage.

Botulinum Toxin

History and Discovery

Botulinum toxin, produced by *Clostridium botulinum,* causes botulism when ingested. The first clinical use of this toxin was in the treatment of childhood strabismus (Scott 1980), and its first use to treat a focal dystonia was with blepharospasm (Elston 1988). Since these first uses, botulinum toxin has been used to treat many other conditions associated with excessive muscle activity, including medication-induced dystonias (Hughes 1994).

Structure-Activity Relations

There are seven immunologically distinct botulinum toxins (Simpson 1981). Type A is the primary type used clinically (Hambleton 1992). Type F and possibly type B also have clinical utility, but they have much shorter durations of action ([?] 3 weeks, compared with [?] 3 months for type A) (Borodic *et al.* 1996). The toxin is quantified by bioassay and is expressed in "mouse units" (i.e., the dose that is lethal to 50% of animals following intraperitoneal injection [Quinn and Hallet 1989]).

Pharmacological Profile

Botulinum toxin binds to cholinergic motor nerve terminals, preventing release of acetylcholine and producing a functionally denervated muscle. Prevention of acetylcholine release occurs within a few hours, but the clinical effect does not occur for 1-

3 days. The innervation is gradually restored, although the number or size of active muscle fibers is reduced (Odergren *et al.* 1994).

Pharmacokinetics and Disposition

After binding to the presynaptic nerve terminal, the toxin is taken into the nerve cell and metabolized. When antibodies are present, the toxin is metabolized by immunological processes.

Mechanism of Action

Botulinum toxin acts presynaptically to prevent the release of acetylcholine at the neuromuscular junction. This blockade produces a functional chemical denervation and paralysis of the muscle. When botulinum toxin is used clinically, the aim is to reduce the excessive muscle activity without producing significant weakness (Hughes 1994).

Indications

The FDA has approved the use of botulinum toxin for strabismus, blepharospasm, and other facial nerve disorders (see Jankovic and Brin 1991). Botulinum toxin is used to treat focal neuroleptic-induced dystonias that may occur as part of TD, including laryngeal dystonia (Blitzer and Brin 1991) and refractory torticollis (Kaufman 1994). For laryngeal dystonia, the toxin is injected percutaneously through the cricothyroid membrane into the thyroarytenoid muscle bilaterally. The response rate is 80%-90%, and the effect lasts 3-4 months and sometimes longer. Botulinum treatment is effective for tardive cervical dystonia; the observed improvement was similar to the improvement seen in the treatment of idiopathic cervical dystonia, although patients with tardive cervical dystonia required higher doses (Brashear *et al.* 1998).

Side Effects and Toxicology

The major potential side effect of botulinum toxin is focal weakness in the injected muscle group, an effect that is usually dose dependent. This effect is generally temporary, given the mechanism of action. Transient weakness also can occur through diffusion of toxin into surrounding noninjected muscles (Hughes 1994).

Antibodies to the toxin can develop and can prevent a therapeutic response, particularly for the next few treatments. The two main factors contributing to the development of antibodies are young age at first treatment with the toxin and total cumulative dose (Jankovic and Schwartz 1995). Some individuals with antibodies will respond to other botulinum serotypes, such as type F (Greene and Fahn 1993). Local skin reactions also can occur. Some degree of muscle atrophy is apparent in injected muscles (Hughes 1994). Reinnervation usually takes place over the course of 3-4 months (Odergren *et al.* 1994).

Botulinum toxin has no known contraindications. Because the effect on the fetus is unknown, use of the toxin is not recommended during pregnancy. In conditions in which there are neuromuscular junction disorders, such as myasthenia gravis, patients could theoretically experience increased weakness. The long-term effects are unknown (Hughes 1994).

Drug-Drug Interactions

Botulinum toxin has no known interactions with other drugs.

Vitamin E (Alpha-Tocopherol) for Tardive Dyskinesia

History and Discovery

Vitamin E was proposed as a treatment for TD after it was noted that administration of a neurotoxin to rats induced an irreversible movement disorder and axonal damage similar to that caused by vitamin E deficiency. It was proposed that long-term antipsychotic use might produce free radicals, which would contribute to neurological damage and TD, and that the antioxidant effect of vitamin E could attenuate the damage (Cadet *et al.* 1986).

Indications

The only known indication for vitamin E is treatment of vitamin E deficiency, which almost always results from malabsorption syndromes or abnormal transport, such as with abetalipoproteinemia (Bieri and Farrell 1976).

Early studies of vitamin E treatment of TD reported findings ranging from general benefit (Adler *et al.* 1993b; Dabiri *et al.* 1994; Lohr *et al.* 1988) to benefit only in subjects with TD of fewer than 5 years' duration (Egan *et al.* 1992; Lohr and Caligiuri 1996) to no benefit (Schmidt *et al.* 1991; Shriqui *et al.* 1992). Subsequently, a major double-blind study comparing vitamin E with placebo found that vitamin E was no more beneficial than placebo (Adler *et al.* 1999). There were no significant effects of vitamin E on total scores or subscale scores on the AIMS (Guy 1976), on electromechanical measures of dyskinesia, or on scores for four other scales measuring dyskinesia. The authors concluded that there was no evidence for efficacy of vitamin E in the treatment of TD (Adler *et al.* 1999).

The use of vitamin E supplementation is not without risk. A meta-analysis of high-dosage vitamin E supplementation trials showed a statistically significant association between vitamin E dosage and all-cause mortality, with increased risk for dosages greater than 150 IU/day (Miller *et al.* 2005). Given the lack of data showing its consistent effectiveness for TD, vitamin E is not recommended for this purpose.

Side Effects and Toxicology

Side effects are minimal when vitamin E is given orally. High levels of vitamin E can exacerbate bleeding abnormalities that are associated with vitamin K deficiency. Dosages of up to 3,200 mg/day in studies for other conditions have been used without significant adverse effects (Kappus and Diplock 1992). The only known drug interactions are with vitamin K (when it is being given for a deficiency and bleeding abnormalities) and possibly with oral anticoagulants. High dosages of vitamin E can exacerbate the coagulation abnormalities in both cases and therefore are contraindicated (Kappus and Diplock 1992).

Vesicular Monoamine Transporter 2 Inhibitor Drugs

History and Discovery

Tetrabenazine, a reversible and specific inhibitor of VMAT2, was initially developed in the 1950s. The use of tetrabenazine as a treatment for TD was first reported in 1972 (Kazamatsuri *et al.* 1972). Subsequently, tetrabenazine was approved for use in treating hyperkinetic movement disorders in several countries, including Canada, France, Germany, Spain, and the UK. In 2008, tetrabenazine received U.S. FDA approval as an orphan drug to treat chorea in Huntington's disease. Efforts to retain the efficacy of tetrabenazine and address its safety profile, including significant akathisia and parkinsonism, led to development of valbenazine and deutetrabenazine, and in 2017, these agents became the first drugs to be approved by the FDA specifically for the treatment of tardive syndromes.

Prior to their approval, valbenazine and deutetrabenazine were evaluated in well-designed randomized, double-blind, placebo-controlled efficacy trials. The primary outcome measure in both trials was the change in the AIMS score, based on ratings of randomized video segments by a central panel of movement disorder specialists who were blinded to treatment assignment. Neither of the trials specified which tardive subtypes were present.

For valbenazine, the Phase II (KINECT2, $n = 100$) (O'Brien *et al.* 2015) and Phase III (KINECT3, $n = 225$) (Hauser *et al.* 2017) studies were randomized, placebo-controlled, double-blind 6-week trials. Subjects received placebo or valbenazine (escalated up to 75 mg/day in KINECT2 and administered in dosages of 40 mg/day or 80 mg/day in KINECT3). DRB agents were continued at stable dosages during the trial. Both studies found that valbenazine treatment, relative to placebo, was associated with a significantly greater dose-dependent reduction in AIMS scores. A 42-week extension study of the KINECT3 trial maintained the valbenazine group on their randomly assigned dosages and re-randomized the placebo-treated subjects to either 40 mg or 80 mg valbenazine daily (Factor *et al.* 2017).

Reductions in AIMS scores continued in all groups over the 42 weeks, and long-term safety was demonstrated. After a 4-week washout of valbenazine, AIMS scores returned to baseline levels.

The two deutetrabenazine studies for treatment of tardive syndrome, each 12 weeks in duration, demonstrated significantly greater reductions in AIMS scores at deutetrabenazine dosages of 24 mg/day or higher compared with placebo. The Phase II ARM-TD study (n = 117) (Fernandez *et al.* 2017) compared placebo against deutetrabenazine (up to 24 mg twice daily). In the Phase III AIM-TD study (n = 298) (Anderson *et al.* 2017), subjects were randomly assigned to placebo or deutetrabenazine 12 mg/day, 24 mg/day, or 36 mg/day.

Structure-Activity Relations

Tetrabenazine, deutetrabenazine, and valbenazine are reversible VMAT2 inhibitors, which is the basis for their mechanism of action in hyperkinetic movement disorders. Following reuptake of monoamine neurotransmitters from the synaptic cleft into the neuron, VMAT2, a key protein found only in central presynaptic neurons, transports cytosolic dopamine, norepinephrine, and serotonin into presynaptic vesicles for synaptic release. VMAT2 inhibition prevents this packaging of monoamines, which are then degraded by MAO. As a result, presynaptic dopamine levels are reduced, as is the overstimulation that leads to involuntary movements. Nonselective VMAT inhibition, such as with reserpine, also inhibits VMAT1, which is localized in both the central and peripheral nervous systems and is associated with peripheral adverse effects including hypotension, bronchospasm, nausea, and vomiting.

Pharmacokinetics and Disposition

Tetrabenazine is metabolized via hepatic isoenzyme CYP2D6 into a-dihydrotetrabenazine and b-dihydrotetrabenazine. The half-life of tetrabenazine is 5-7 hours, necessitating dosing three times daily. Its side-effect profile and need for frequent dosing restricted use of tetrabenazine and led to the development of the novel VMAT2 inhibitors valbenazine and deutetrabenazine. Valbenazine was developed as a purified prodrug of dihydrotetrabenazine linked to a valine molecule, which prolongs its half-life for 15-22 hours and allows for once-daily dosing. The limited range of active metabolites of valbenazine reduces off-target binding, as is seen with tetrabenazine. In deutetrabenazine, hydrogen in tetrabenazine is replaced with deuterium, a nonradioactive isotope that renders the drug more resistant to hepatic isoenzymes. As a result, clearance is slower and peak concentrations of tetrabenazine are lower, providing a basis for the increased tolerability of deutetrabenazine and its reduced side effects. The half-life of deutetrabenazine is 9-10 hours, and dosing is twice daily.

Indications and Dosing

Valbenazine and deutetrabenazine are the only drugs approved by the FDA specifically for the treatment of TD. Tetrabenazine was approved in 2008 for the treatment of chorea in Huntington's disease and has been used off-label for TD. Deutetrabenazine was approved in 2017 for the treatment of chorea in Huntington's disease.

When used to treat tardive syndromes, valbenazine and deutetrabenazine differ in their dosing frequency, contraindications, warnings/precautions, drug interactions, and cost. Although no trials have directly compared valbenazine and deutetrabenazine, systematic reviews and meta-analyses have demonstrated that the two drugs have comparable efficacy in reducing AIMS scores and similar tolerability (Artukoglu *et al.* 2020; Patel *et al.* 2019; Solmi *et al.* 2018). The recommended dosage range for valbenazine is 40-80 mg/day given once daily, and that for deutetrabenazine is 6-48 mg/day divided into two doses. Because of its rapid metabolism, tetrabenazine needs to be started at a low dosage (12.5-25 mg/day) and titrated upward with monitoring for adverse effects. A typical therapeutic dosage of tetrabenazine is 50-75 mg/day divided into three doses.

Side Effects and Toxicology

Common adverse effects of VMAT2 inhibitors include somnolence, depression, parkinsonism, and akathisia. Valbenazine has also been associated with dry mouth, dizziness, and headache, and deutetrabenazine with insomnia and nasopharyngitis. All three VMAT2 inhibitors have warnings and precautions for parkinsonism, sedation/somnolence, and QTc prolongation. Individuals taking deutetrabenazine or tetrabenazine should be monitored for depression and suicidality; NMS; akathisia, restlessness, and agitation; hyperprolactinemia, and binding to melanin-containing tissues. In addition, tetrabenazine can cause hypotension and orthostatic hypotension.

Drug-Drug Interactions

The presence of hepatic impairment requires care in the choice of VMAT2 inhibitor for TD management. The three VMAT2 inhibitors have significant drug-drug interactions with strong CYP2D6 inhibitors and monoamine oxidase inhibitors. Additionally, valbenazine interacts with strong CYP3A4 inhibitors and CYP3A4 inducers and digoxin. Deutetrabenazine and tetrabenazine also have significant interactions with reserpine, alcohol and sedating drugs, antipsychotic agents, and concomitant VMAT2 inhibitors. Tetrabenazine has significant interactions with drugs causing QTc prolongation.

Conclusion

Drug-induced movement disorders are a significant complication of psychiatric and nonpsychiatric medications that can be disfiguring, distressing, and even life-threatening. Accurate diagnosis of these iatrogenic conditions requires characterization of the movement phenomena and careful history-taking regarding medication use, duration of exposure to potentially causative agents, and timing of the onset of the movement abnormality relative to the medication exposures. Even though antipsychotic medications are typically cited as culprits of acute dystonia, acute akathisia, drug-induced parkinsonism, and tardive syndromes, commonly used mood stabilizers and antidepressants and nonpsychiatric medications also cause abnormal movements and warrant attention. Prudent prescribing practices, patient and caregiver education, visual observation of the patient, and systematic serial assessments are the cornerstones of prevention and early identification of drug-induced movement disorders. When required, treatment begins with dosage reduction or cessation of the offending agents when possible. Accurate diagnosis further guides treatment, especially when multiple movement subtypes are present. For each subtype of movement abnormality, there is a limited range of pharmacological treatments with variable efficacy, and treatment decisions are often based on analysis of risks and likely benefits. The relatively recent development of valbenazine and deutetrabenazine provides effective and safe interventions for tardive syndromes. It is hoped that new drug development, especially for antipsychotics, will focus on medications with reduced liability to cause drug-induced movement disorders.

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Drugs for Treatment of Bipolar Disorder

CHAPTER 37

Lithium

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History and Discovery

After noting the sedating properties of lithium in animals, Cade (1949) first described the successful treatment of mania with lithium salts. The FDA approved lithium for the treatment of acute mania in 1970 and for the maintenance treatment of bipolar disorder 4 years later (Jefferson and Greist 1977). However, lithium did not enter the market easily in the United States. Pharmaceutical companies were reluctant to produce this inexpensive drug that they could not patent (Kline 1973). Lithium is available generically and is inexpensive, which, added to its effectiveness, has given it longevity among the psychopharmacological treatment options for bipolar disorder (Chisholm *et al.* 2005).

Structure-Activity Relations

Lithium is the lightest alkali metal and a monovalent cation, and it shares some properties with sodium, potassium, and calcium. It is the third element of the periodic table. Substitution of or competition with other cations may contribute to its effects (Baldessarini 1996; Ward *et al.* 1994).

Pharmacological Profile

Lithium is minimally protein bound, does not undergo biotransformation, and is eliminated by the kidneys (Kilts 2000). Its narrow therapeutic index necessitates careful drug monitoring. Lithium appears to affect multiple neurotransmitter systems (see "Neurotransmitter Effects" subsection under "Mechanism of Action"), and it alters second-messenger systems such as cyclic adenosine monophosphate and cyclic guanosine monophosphate (Ward *et al.* 1994).

Pharmacokinetics and Disposition

Lithium is available in multiple preparations, including lithium carbonate tablets and capsules, lithium citrate solution, and slow-release tablet formulations (Jefferson *et al.* 1983). Immediate-release lithium carbonate capsules are marketed in strengths of 150 mg, 300 mg, and 600 mg, whereas immediate-release lithium carbonate tablets are available in only a single strength of 300 mg. Lithium citrate oral solution is available at a concentration of 300 mg/5 mL, which is considered equivalent to the 300-mg lithium carbonate immediate-release tablets and capsules. The extended-release lithium carbonate tablet formulation is available in 300-mg and 450-mg strengths. Generic equivalent products are available for all of these formulations (West-Ward Pharmaceuticals 2018).

Lithium is absorbed from the gastrointestinal tract and is renally excreted unchanged within approximately 24 hours (Baldessarini 1996). Peak plasma concentrations are reached in 0.25-3.00 hours with the immediate-release preparations and in 2-6 hours with the extended-release formulation (Finley *et al.* 1995; West-Ward Pharmaceuticals 2018). Lithium is not protein bound and is evenly distributed in total body water space (Jermain *et al.* 1991). Lithium excretion is controlled by osmotic factors and is a function of renal sufficiency (Birch *et al.* 1980). Steady-state concentrations are achieved in 4-5 days (Keck and McElroy 2002).

Mechanism of Action

Despite extensive research, the exact mechanism of lithium's action as a mood stabilizer has yet to be elucidated. Multiple theories, based on animal models and on limited studies in humans, have been proposed. In the following pages we review theories centering on lithium's effects on various neurotransmitter systems, on intracellular second-messenger systems, and on signal transduction, as well as a unifying theory focused on lithium's neuroprotective effects.

Neurotransmitter Effects

Lithium brings about changes in several of the major neurotransmitter systems in the brain, with the overall effect being stimulation of inhibitory transmission and inhibition of excitatory signals (Malhi *et al.* 2013). Chronic administration of lithium in mice increases and stabilizes glutamate uptake. This modulatory action could, in part, explain lithium's antimanic effect because it results in overall reduction of an excitatory neurotransmitter (Dixon and Hokin 1998). Lithium also normalizes low cerebrospinal fluid (CSF) levels of GABA (an inhibitory neurotransmitter) in patients with bipolar disorder (Berrettini *et al.* 1983, 1986; Brambilla *et al.* 2003).

Lithium enhances norepinephrine and serotonin function in the CNS, which could explain its antidepressant effects (Price *et al.* 1990; Schildkraut *et al.* 1969; Stern *et al.* 1969). Of particular interest is lithium's confirmed antagonistic action at serotonin$_{1A}$ (5-HT$_{1A}$) and serotonin$_{1B}$ (5-HT$_{1B}$) autoreceptors (Haddjeri *et al.* 2000; Massot *et al.* 1999); such action would have the effect of increasing serotonin availability in the synaptic cleft (Shaldubina *et al.* 2001). Clinically, 5-HT$_{1A}$ receptors may be involved in alleviation of depression, and 5-HT$_{1B}$ receptors may play a role in the regulation of sleep, sensorimotor inhibition, and locomotor activity (Monti *et al.* 1995; Sipes and Geyer 1996).

Inositol Depletion

There has been much focus on the role of the inositol cycle in the clinical effects of lithium. Lithium is a noncompetitive inhibitor of inositol monophosphatase, depleting free inositol within 5 days of treatment initiation (Berridge *et al.* 1989). These changes last for 3-4 weeks after lithium is discontinued (Moore *et al.* 1999). Depletion of free inositol can lead to effects on neurotransmitter and intracellular second-messenger systems linked to the inositol cycle. For example, adrenergic, serotonergic, and cholinergic receptor subtypes are coupled to the cycle via G proteins, and the cycle in turn regulates protein kinase C action, which appears to be influenced by lithium treatment in mania (Hahn *et al.* 2005).

Of note, depression is associated with low CSF levels of inositol in humans (Barkai *et al.* 1978). Exogenous inositol can alleviate depression (Levine *et al.* 1995) and panic attacks (Benjamin *et al.* 1995). Belmaker *et al.* (1996) suggested a complex "pendulum" relationship between inositol and lithium that may provide a basis for understanding lithium's antimanic and antidepressant effects.

Glycogen Synthase Kinase Inhibition

Glycogen synthase kinase 3 (GSK-3) is an enzyme with direct involvement in gene transcription, synaptic plasticity, and cell structure (Malhi *et al.* 2013). Both lithium (Klein and Melton 1996; Li *et al.* 2007) and valproate inhibit GSK-3, suggesting that signaling pathways that converge in GSK-3 are important in bipolar disorder (G. Chen *et al.* 1999). GSK-3 is an inhibitor of the Wnt protein-signaling pathway, which affects neuronal signal transduction. Lithium thus would be predicted to mimic Wnt signaling (Phiel and Klein 2001). Wnt signaling triggers a cascade of events that lead to stimulation of protein kinase C activity (Williams and Harwood 2000). Thus, the actions of lithium on both the inositol cycle and the GSK-3 signaling pathway lead to a common effect on protein kinase C. Because this enzyme's activity has been reported to be elevated in bipolar disorder, protein kinase C inhibitors have been investigated for their potential treatment utility (Zarate and Manji 2009).

Neurotrophic and Neuroprotective Effects

A unifying theory posits that lithium's mechanism of action may be related to its neurotrophic and neuroprotective effects (Quiroz *et al.* 2010). Patients treated with lithium have larger cortical and hippocampal volumes (Hajek *et al.* 2012, 2014; Moore *et al.* 2000), and these effects are independent of treatment response (Hajek *et al.* 2014). One proposed mechanism is lithium's activation of the transcription factor cyclic adenosine monophosphate response element binding protein, which in turn increases the expression of brain-derived neurotrophic factor and the antiapoptotic B-cell lymphoma 2 proteins (Alda 2015; Quiroz *et al.* 2010). Another proposed mechanism is lithium's inhibition of GSK-3 and subsequent activation of the Akt neuroprotective pathway (Tajes *et al.* 2009).

Pharmacogenetics of Lithium Response in Bipolar Disorder

Pharmacogenetics of response to lithium is an important aspect of precision medicine aimed at predicting response and tolerability in bipolar disorder. Several reviews on the topic have been published (Cruceanu *et al.* 2009; Lin *et al.* 2021; McCarthy *et al.* 2010; Oedegaard *et al.* 2016; Serretti and Drago 2010; Smith *et al.* 2010; Vecera *et al.* 2021). Vecera *et al.* (2021), in their recent review, discussed six genomewide association studies that each included at least 250 subjects for statistical considerations. Genes regulating the glutamate system (e.g., *GADL1* and *GRIA2*) were associated with lithium response (Chen *et al.* 2014; Perlis *et al.* 2009). Moreover, the authors found that genetic risk for schizophrenia and major depressive disorder has an inverse relationship to lithium responses in bipolar disorder (Amare *et al.* 2018, 2021). A single-nucleotide polymorphism on *SESTD1* may be related to lithium's ability to permeate cell membranes and mediate autoimmune and renal effects (Song *et al.* 2016). Furthermore, epigenetics and stress regulation of long noncoding RNA genes and human leukocyte antigen (HLA) genes were associated with lithium response (Amare *et al.* 2018; Hou *et al.* 2016).

Precision medicine in bipolar disorder is still in its infancy, and replication in independent cohorts is necessary before it can be used in real-world clinical applications. Precision medicine for this indication is likely to include not only genetics but also other biomarkers, such as neuroimaging (Athey *et al.* 2021; Fleck *et al.* 2017; Rootes-Murdy *et al.* 2019), and epigenetic markers (Marie-Claire *et al.* 2020).

Indications and Efficacy

Immediate-release lithium dosage forms are indicated as monotherapy for the treatment of bipolar disorder. This indication includes treatment of acute manic and mixed episodes and maintenance treatment in patients ages 7 years and older (West-Ward Pharmaceuticals 2018). Extended-release lithium tablets are indicated for treatment of manic episodes and maintenance treatment in patients 12 years and older with a diagnosis of bipolar disorder (Glenmark Pharmaceuticals 2022).

Bipolar Disorder

Acute Mania

Cade (1949) first published data on the efficacy of lithium in mania. More than 70 years later, lithium remains one of the most efficacious treatments for bipolar disorder and, according to contemporary treatment guidelines, should be considered first for acute mania, with certain exceptions, such as presence of mixed features, comorbid substance use, or prior treatment nonresponse (Yatham *et al.* 2018).

Lithium versus placebo. Lithium has been shown in studies to be more efficacious than placebo in the treatment of acute mania (Bowden *et al.* 1994, 2005; Fountoulakis *et al.* 2012; Goodwin *et al.* 1969; Keck *et al.* 2009; Kushner *et al.* 2006; Poolsup *et al.* 2000; Schou *et al.* 1954; Smith *et* *al.* 2007; Yildiz *et al.* 2011). A review of response rates in randomized trials of medication treatment indicated that lithium was at least somewhat efficacious in the treatment of mania, with a response rate of 70% (87 of 124 patients) (Keck *et al.* 2000). A more recent review of pharmacological treatment of bipolar disorder (Baldessarini *et al.* 2019) demonstrated an overall response rate of 49.1% (95% CI: 42.8%-55.3%) for lithium in placebo-controlled trials in patients with acute mania, a rate similar to that for other treatment types.

Lithium versus antipsychotics. Early studies with lithium established its antimanic efficacy relative to first-generation (typical) antipsychotics (Johnson *et al.* 1968; Poolsup *et al.* 2000; Prien *et al.* 1972; Segal *et al.* 1998; Shopsin *et al.* 1975; Spring *et al.* 1970; Takahashi *et al.* 1975). A study by Prien *et al.* (1972) comparing lithium against chlorpromazine found that although chlorpromazine was more effective in reducing manic symptoms in severely ill patients, lithium also reduced symptoms while causing fewer side effects. However, a later meta-analysis concluded that lithium was more effective than chlorpromazine in acute mania (Poolsup *et al.* 2000). Segal *et al.* (1998) reported that hospitalized patients with acute mania responded equally well to lithium, haloperidol, and the second-generation agent risperidone.

Lithium has also been studied in comparison with second-generation antipsychotic medications (Berk *et al.* 1999; Bowden *et al.* 2005; Fountoulakis *et al.* 2012; Keck *et al.* 2009; Niufan *et al.* 2008; Poolsup *et al.* 2000; Segal *et al.* 1998; Smith *et al.* 2007; Yildiz *et al.* 2011). However, many of these trials were focused on assessing the efficacy of the antipsychotic in a noninferiority approach rather than on demonstrating significant differences between the medications. For example, in a direct comparison with lithium, olanzapine produced greater improvement in manic symptoms over a period of 4 weeks, but it also produced more weight gain (Niufan *et al.* 2008). By and large, antipsychotics appear to work faster than lithium but carry higher risks for weight gain and other metabolic effects (Fountoulakis *et al.* 2012; Yildiz *et al.* 2011). The addition of lithium to therapy with extended-release quetiapine was found to be more efficacious than add-on placebo (i.e., quetiapine monotherapy) for patients with bipolar mania (Bourin *et al.* 2014). A 2019 systematic review of lithium for acute mania (McKnight *et al.* 2019), which included 36 randomized controlled trials and 4,220 patients, found that lithium is not inferior to antipsychotics, although it may be less likely than olanzapine to induce a response (defined as 50% reduction in symptoms on the Young Mania Rating Scale); however, the quality of evidence supporting this finding was not high.

Lithium versus anticonvulsants. Double-blind randomized studies suggest that carbamazepine and lithium are equally effective in the treatment of acute mania (Fountoulakis *et al.* 2012; Lerer *et al.* 1987; Okuma *et al.* 1990; Poolsup *et al.* 2000; Small *et al.* 1991; Yildiz *et al.* 2011). In a direct comparison of lithium and divalproex, Bowden *et al.* (1994) demonstrated a similar advantage for both agents over placebo, with lithium and divalproex each achieving response in about 48% of patients over 3 weeks. A 12-week study of patients randomly assigned to open treatment with lithium or divalproex yielded additional evidence of the two agents' comparable efficacy

and tolerability over a longer-than-usual study period (Bowden *et al.* 2008, 2010a). Various meta-analyses and systematic reviews examining the efficacy of lithium, valproate, and carbamazepine in mania have shown no significant differences (Poolsup *et al.* 2000; McKnight *et al.* 2019).

Mixed States

The presence of mixed features--co-occurrence of depressive and manic symptoms--may predict a poorer response to lithium monotherapy. Freeman *et al.* (1992), in a direct comparison of lithium and valproate, showed that high pretreatment depressive symptom scores were associated with a favorable response to valproate (Fountoulakis *et al.* 2012). To further investigate the relation between co-occurring depressive symptoms and treatment response in acute mania, Swann *et al.* (1997) designed a parallel-group study of lithium versus divalproex and analyzed outcomes relative to the presence of a mixed affective state. They found that the presence of depressive symptoms during an acute manic episode was associated with a poorer response to lithium and a better response to divalproex. Existing reviews assessing the efficacy of treatment strategies for mixed states (McIntyre and Yoon 2012; Takeshima 2017) suggest combination therapy including atypical antipsychotics and conventional mood stabilizers such as lithium or valproate have the most replicated evidence; additional studies are needed to better understand lithium's degree of efficacy, and the high rate of attempted suicide in mixed states may make lithium a reasonable treatment option that should not be overlooked.

Psychotic Mania

Lithium is equally effective in psychotic and nonpsychotic mania, and early improvement in psychotic symptoms was found to predict higher remission and response rates (de Sousa *et al.* 2012).

Bipolar Depression

Lithium is considered a first-line treatment for acute bipolar depression (Compton and Nemeroff 2000; Yatham *et al.* 2018). Placebo-controlled trials showing the efficacy of lithium in bipolar depression include those by Baron *et al.* (1975), Donnelly *et al.* (1978), Fieve *et al.* (1968), Goodwin *et al.* (1969, 1972), Greenspan *et al.* (1970), and Noyes *et al.* (1974).

A meta-analytic summary of the above-listed short-term studies showed a significant advantage for lithium over placebo in bipolar disorder (Selle *et al.* 2014). In the Efficacy of Monotherapy Seroquel in BipOLar DEpressioN (EMBOLDEN) I study, in which in 802 patients were randomly assigned to 8 weeks of treatment with lithium (600-1,800 mg/day), quetiapine (300 mg/day or 600 mg/day), or placebo (Young *et al.* 2010), lithium failed to separate significantly from placebo on the main efficacy measure (Montgomery-Asberg Depression Rating Scale score); however, the study was powered to show an effect for quetiapine, and the mean serum level in lithium-treated subjects was low (0.6 mEq/L).

In the Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) trial, 482 patients with bipolar I or II disorder, the majority (> 88%) of whom were experiencing depressive symptoms at study entry (Nierenberg *et al.* 2016), were randomly assigned to receive lithium plus adjunctive personalized treatment ($n = 240$) or quetiapine plus adjunctive personalized treatment ($n = 242$) for 6 months. In this study, which used new clinical trial methodology, participants in the lithium group were not given a second-generation antipsychotic, and those in the quetiapine group were not given lithium; however, other adjunctive treatments were provided in accordance with best-practice guidelines (Nierenberg *et al.* 2013). Both groups showed improvement, with 20% achieving sustained response over the study period, and no differences in outcome were detected between the lithium and quetiapine groups.

In the Lithium Treatment Moderate-Dose Use Study (LiTMUS; Nierenberg *et al.* 2013), 283 patients with bipolar I or II were randomly assigned to receive optimized personalized treatment (OPT; evidence-based, guideline-informed care) alone or OPT plus lithium at a moderate dosage. The lithium dosage was fixed at 600 mg/day for the first 2 months of the study but was allowed to change based on clinical need after that. Over the 6 months of the trial, the two groups had similar scores on clinical outcome measures, with a sustained remission rate of 27%. Although the addition of lithium conferred no advantage over OPT alone, fewer patients in the lithium-plus-OPT group than in the OPT-only group received second-generation antipsychotics.

Rapid Cycling

In 1974, Dunner and Fieve observed that patients with bipolar disorder who had not responded to long-term lithium prophylaxis were more likely to have had four or more mood episodes per year, giving rise to the belief that lithium is not effective in treating rapid cycling. However, subsequent studies have shown that rapid-cycling bipolar disorder responds poorly to most available treatments and that treatment with lithium does reduce the burden of illness. In a study examining lithium's efficacy in rapid-cycling bipolar disorder, Dunner *et al.* (1977) found that patients who had received lithium for at least 1 year had a higher percentage of "well time" relative to baseline and reported that their mood episodes were shorter and less severe. A long-term prospective study of open-label treatment with lithium found a higher rate of recurrence among rapid cyclers than non-rapid cyclers but similar improvement in symptoms and morbidity (as measured by percentage of time ill, episode frequency, and time to recurrence) (Baldessarini *et al.* 2000). Finally, a meta-analysis of clinical studies comparing subjects with rapid-cycling and non-rapid-cycling bipolar disorder showed that although lithium was less effective in preventing recurrence among rapid cyclers, it did have beneficial effects on severity and duration of episodes (Kupka *et al.* 2003). In a 20-month double-blind, parallel-group comparison study, Calabrese *et al.* (2005) evaluated lithium and divalproex monotherapy for maintenance treatment of rapid-cycling patients who had been stabilized on a combination of lithium and divalproex. The rates of relapse were similar for lithium-treated and divalproex-treated patients.

Prophylaxis and Maintenance

Prophylactic or maintenance therapy aims to prevent the recurrence of future depressive and hypomanic episodes. Lithium is considered a first-line treatment for this indication (Yatham *et al.* 2018).

Numerous systematic reviews and meta-analyses have synthesized the outcomes of placebo-controlled trials involving lithium for maintenance therapy and found lithium's efficacy in preventing relapse of mood episodes to be statistically significant,

with more protection afforded to prevention of mania than depression (Baldessarini *et al.* 2019; Beynon *et al.* 2009; Davis *et al.* 1999; Geddes *et al.* 2004).

Tondo *et al.* (1998a) found lithium to be effective in long-term use (> 1 year) in decreasing frequency of mood episodes and time ill in patients with bipolar I or bipolar II disorder. Benefits of lithium treatment were not significantly different among patients with psychotic or mixed episodes, rapid cycling, or more classic forms. There was no decrease in efficacy with long-term use. Despite finding evidence for lithium's efficacy, Kulhara *et al.* (1999) noted that only 24% of the patients followed in a lithium clinic remained free of mood episodes while receiving lithium prophylaxis (average duration of monitoring: 11 years). Treatment nonadherence or subtherapeutic lithium serum levels (< 0.4 mEq/L), high numbers of psychosocial stressors, higher numbers of depressive episodes before lithium treatment, and poor social support predicted poorer response to lithium prophylaxis. In contrast, starting lithium early in the course of illness predicted a better response to treatment ($P < 0.001$), after episode polarity, sex, age at onset, duration of illness, and duration of lithium prophylaxis were accounted for (Franchini *et al.* 1999).

Bowden *et al.* (2003) compared the efficacy of lamotrigine, lithium, and placebo in preventing relapse to mood episodes among subjects with bipolar I and a recent manic or hypomanic episode. After completing a stabilization phase during which treatment with lamotrigine was initiated and other medications were discontinued, subjects were randomly assigned to one of the three drug groups and followed for 18 months. Both lithium and lamotrigine were superior to placebo in prolonging the time to any mood episode, with lithium predominantly effective against manic, hypomanic, and mixed episodes and lamotrigine predominantly effective against depressive episodes. A similar study in subjects with bipolar I and a recent depressive episode (Calabrese *et al.* 2003) reported the same findings. A post hoc analysis of the two studies revealed that lithium not only prolonged the time between random assignment and onset of subsyndromal symptoms but also prolonged the time between onset of subsyndromal symptoms and emergence of the full mood episode (Frye *et al.* 2006). In a study by Weisler *et al.* (2011), subjects with bipolar disorder who had been stabilized on quetiapine were randomly assigned to continue quetiapine or be switched to lithium or placebo for up to 104 weeks. Both lithium and quetiapine were superior to placebo in prevention of manic and depressive episodes.

The Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) study examined the effects of lithium monotherapy, valproate monotherapy, or lithium-plus-valproate combination therapy for relapse prevention in a large international cohort (BALANCE Investigators and Collaborators 2010). More than 300 patients with bipolar I disorder initially completed a "run-in" phase during which they took both lithium and valproate. Of those who tolerated the combination, a subsequent randomization phase assigned subjects to lithium alone, valproate alone, or continued combination treatment for up to 2 years of follow-up. The primary outcome measure was time to new intervention (either medication change or hospitalization) for an emerging mood episode. The study results showed that the combination of lithium and valproate was superior to valproate alone and suggested that lithium monotherapy was superior to valproate monotherapy. However, the apparent discrepancy between these findings and the conclusions of Bowden *et al.* (2010a) may reflect differences in the population studied, the outcome measures used, or a suboptimal valproate dosage in the BALANCE

study. In a double-blind, randomized maintenance trial of lithium versus olanzapine, individuals with bipolar disorder experiencing mixed or manic symptoms first received open-label cotreatment with lithium and olanzapine (Tohen *et al.* 2005). Those whose symptoms remitted were then randomly assigned to monotherapy with either lithium or olanzapine for 52 weeks. Recurrence rates were similar for the two groups, with 38.8% of patients on lithium and 30.0% of those on olanzapine experiencing a relapse. Whereas the two drugs were comparable in prevention of depressive episodes, olanzapine was more effective than lithium in prevention of manic and mixed episodes.

Maintenance dosing. Once-daily dosing of lithium at bedtime yields higher brain-to-serum ratios of lithium levels compared with twice-daily dosing schedules (Soares *et al.* 2001). Investigators have observed substantial variations in brain lithium levels among people with similar serum lithium levels (Gonzalez *et al.* 1993). In a study evaluating maintenance treatment with lithium at dosages yielding low (0.4-0.6 mEq/L) versus standard (0.8-1.0 mEq/L) serum levels, Gelenberg *et al.* (1989) found that the risk of relapse was 2.6 times higher in patients randomly assigned to maintenance lithium at the low serum level. However, in a reanalysis of the data (Perlis *et al.* 2002), the higher relapse rate observed with the low serum level was found to be associated with the abrupt reduction in lithium dosage that occurred after randomization in patients who were switched from the standard range to the low range. Thus, an abrupt reduction in lithium dosage may negatively affect the course of illness.

Nolen and Weisler (2013) conducted a post hoc analysis of a double-blind trial of patients with bipolar disorder who were stabilized on quetiapine after a manic, depressive, or mixed episode and then randomly assigned to continue quetiapine or be switched to lithium or placebo for up to 104 weeks. Times to recurrence of any mood episode, as well as to recurrence of a manic or a depressive episode, were longer for patients with serum lithium levels of 0.6-1.2 mEq/L than for patients with serum lithium levels less than 0.6 mEq/L. No difference in time to recurrence was found between patients receiving placebo and patients with lithium levels lower than 0.6 mEq/L, providing evidence that maintenance lithium dosages should be high enough to achieve a plasma level of at least 0.6 mEq/L for prevention of mania and depressive episodes in bipolar disorder. In a similar post hoc analysis by Severus *et al.* (2010), subjects were first stabilized on a combination of lithium and olanzapine and then randomly assigned to lithium (at dosages aimed at achieving low [0.6 mEq/L)], medium [0.6-0.79 mEq/L], or high [> 0.8 mEq/L] serum levels) or olanzapine (10 mg/day or 10-20 mg/day) for the maintenance phase. The low-serum-level lithium group had a significantly higher risk of relapse to manic or mixed--but not to depressive--episodes compared with the medium-and high-serum-level lithium groups and had a higher risk of depression than the 10-20 mg/day olanzapine group. These findings provide further evidence that lithium levels should be higher than 0.6 mEq/L for optimal protection against relapse to manic, mixed, or depressive episodes.

Unipolar Depression (Major Depressive Disorder)

An analysis of five controlled trials of lithium augmentation of antidepressant treatment for patients with unipolar depression found significant improvement in 56%-96% of patients (Austin *et al.* 1991; Carvalho *et al.* 2009; Heit and Nemeroff 1998;

Heninger *et al.* 1983; Kantor *et al.* 1986; Schopf *et al.* 1989; Stein and Bernadt 1993; Zusky *et al.* 1988). Two separate meta-analyses of randomized, double-blind, placebo-controlled trials in unipolar and bipolar depression evaluated lithium's efficacy in augmenting and accelerating clinical response to antidepressant treatment (Crossley and Bauer 2007). Although there was firm evidence of lithium's efficacy as an augmentation agent, there was only modest evidence of its efficacy in accelerating response to antidepressants. Concordant with previous reviews (Abou-Saleh *et al.* 2017; Bauer *et al.* 2010; Nelson *et al.* 2014), a recent systematic review (Undurraga *et al.* 2019) and selective random-effects meta-analysis of 12 randomized controlled trials of lithium augmentation of antidepressants for acute unipolar major depressive disorder found a highly significant pooled outcome (OR: 2.34; 95% CI: 1.57-3.51; $P < 0.0001$) favoring lithium over placebo, with even more robust effect in studies involving treatment-resistant depression, despite the fact that only 4 out of the 12 trials found significant efficacy for lithium on an individual basis.

In treatment-refractory depression, open-label data support the addition of lithium to antidepressants, including tricyclic antidepressants, trazodone, and selective serotonin reuptake inhibitors (SSRIs) (Bschor *et al.* 2001; De Montigny *et al.* 1981, 1983, 1985; Dinan 1993; Fontaine *et al.* 1991; Price *et al.* 1986). Double-blind and open-label studies support the use of lithium for augmentation of tricyclic antidepressants, monoamine oxidase inhibitors, trazodone, mirtazapine, and SSRIs (Baumann *et al.* 1996; Fava *et al.* 1994; Heninger *et al.* 1983; Joffe *et al.* 1993; Kantor *et al.* 1986; Katona *et al.* 1995; Nierenberg *et al.* 2006; Schopf *et al.* 1989; Schule *et al.* 2009; Zusky *et al.* 1988). In the large Sequenced Treatment Alternatives to Relieve Depression multisite trial, 15.9% of subjects who did not experience remission with citalopram monotherapy and another medication trial achieved remission after the addition of lithium (Nierenberg *et al.* 2006).

Single studies have found that severe depression (Bschor *et al.* 2013), weight loss and psychomotor retardation (Alvarez *et al.* 1997), more than three lifetime major depressive episodes, and a family history of major depressive or bipolar disorder in a first-degree relative (Sugawara *et al.* 2010) may predict a good response to lithium augmentation in treatment-resistant depression. These studies are limited by small heterogeneous samples, variations in treatment duration, use of mostly nonblinded, retrospective study designs, and absence of a placebo comparator.

Timing of onset of lithium action when the drug is used as an adjunct to antidepressant treatment remains unclear. A meta-analysis of placebo-controlled trials of lithium augmentation in treatment-resistant depression found that a minimum lithium dosage of 800 mg/day (or dosing to produce a serum level of [?] 0.5 mEq/L) and a treatment duration of at least 2 weeks favored lithium augmentation as compared with placebo (Bauer and Dopfmer 1999).

Suicide: Is Lithium Protective?

Tondo *et al.* (2021) estimated that up to 60% of people living with bipolar disorder attempt suicide during their lifetime, and suicide fatalities occur in 5%-20% of adults with bipolar disorder. Meta-analyses of studies of lithium treatment in major mood disorders (Baldessarini *et al.* 2006; Cipriani *et al.* 2013; Guzzetta *et al.* 2007; Tondo *et al.* 1998b, 2001) found significantly lower suicide risk for subjects who were receiving treatment with lithium. A meta-review by Smith and Cipriani (2017) identified 16 systematic reviews and meta-analyses published since 2001 of lithium and suicide rates in major mood disorders, which despite some methodological concerns and heterogeneity among studies overwhelmingly support the antisuicidal effects of lithium. Yet specific, placebo-controlled conditions in randomized trials designed to investigate the effects of lithium treatment on suicidality are sparse, in part for various ethical, practical, and financial reasons (Tondo and Baldessarini 2018). The low event rate of suicide is a barrier to conducting adequately powered trials; however, several large-scale observational studies have found a reduced incidence of completed suicide among individuals on lithium treatment, consistent with the evidence from existing randomized data (Roberts *et al.* 2017).

Abrupt discontinuation of lithium treatment is associated with increased rates of suicidal behavior. The antisuicidal effect of lithium appears to be independent of its mood-stabilizing actions (Tondo *et al.* 2021).

A systematic review by Del Matto *et al.* (2020) included 16 ecological studies, 11 of which found a significant inverse association between levels of lithium in drinking water and suicide rates, supporting the growing evidence that routine consumption of lithium in tap water may have antisuicidal effects in the general population.

Use in Special Populations

Children and Adolescents

Lithium is FDA approved for the treatment of bipolar disorder in adolescents and has been shown to be significantly more efficacious than placebo for both bipolar disorder and substance abuse in this population, but not for major depressive disorder (Findling *et al.* 2015; Geller *et al.* 1998a, 1998b; Ryan *et al.* 1999). Lithium had a large effect size in an open-label study of acute manic or mixed episodes in children and adolescents (Kowatch *et al.* 2000) and in an open-label study of acute depressive episodes in adolescents with bipolar I disorder (Patel *et al.* 2006), and it had a medium effect size in a randomized, placebo-controlled study of acute manic or mixed episodes in children and adolescents with bipolar I disorder (Findling *et al.* 2015). In a randomized, double-blind maintenance trial of lithium versus divalproex in children and adolescents ages 5-17 years (Findling *et al.* 2005), lithium-treated patients and divalproex-treated patients did not differ in time to relapse. However, in the Treatment of Early Age Mania study, risperidone was more effective than lithium or divalproex in children ages 6-15 years, whereas there was no difference in efficacy between lithium and divalproex. The incidence of metabolic side effects was higher with risperidone than with lithium, but the discontinuation rate was higher with lithium than with risperidone (Geller *et al.* 2012).

Older Adults

Lithium has shown effectiveness in older adults. In a retrospective trial, significantly more patients age 55 years or older improved with lithium than with valproate, especially in cases of classic mania, whereas the two drugs had similar response rates when the analysis considered only cases of mixed mania (S. T. Chen *et al.* 1999). The lithium serum level range associated with improvement in older adults was similar

to the therapeutic range in younger adults: [?] 0.8 mEq/L (other studies recommend a target dosage [?] 0.4 mEq/L [Nolen *et al.* 2019; Yatham *et al.* 2018]).

Medical comorbidity may be a particular consideration for older adults. Volume depletion, use of nonsteroidal anti-inflammatory drugs (NSAIDs), or use of thiazide diuretics can increase lithium levels (Stoudemire *et al.* 1990). The lithium dosage needed to achieve therapeutic serum concentrations decreases threefold from middle to old age, with this trend continuing into the ninth and tenth decades of life (Rej *et al.* 2014b). In a population-based retrospective cohort study involving 1,388 patients with bipolar disorder ages 66 years and older, medical hospitalizations, 1-year acute medical health utilization outcomes, and medical comorbidity rates were not different between lithium users and valproate users or lithium/valproate nonusers at 1-year follow-up (Rej *et al.* 2015).

Meta-analyses show that lithium is associated with increased risk of reduced urinary concentrating ability, but there is little evidence for a clinically significant reduction in renal function in most patients, and the risk of end-stage renal failure is low (McKnight *et al.* 2012). In one study, lithium use was associated with an increased risk of renal failure among adults ages 50 years and above (Rej *et al.* 2014a). However, chronic lithium use at lower dosages did not affect renal function in older adults with mild cognitive impairment and dementia over a 4-year study period (Aprahamian *et al.* 2014). Because lithium is cleared almost exclusively by the kidneys, patients with end-stage renal disease undergoing hemodialysis cannot eliminate lithium other than through dialysis. Lithium should be given only after a dialysis treatment and need not be given daily (Stoudemire *et al.* 1990).

Because lithium appears to have neuroprotective effects that may reduce oxidative damage, its potential role in prevention of neurocognitive decline in aging and prevention of Alzheimer's disease has been suggested (Mohammadianinejad *et al.* 2014; Shao *et al.* 2005; Tsaltas *et al.* 2007;

Yoshida *et al.* 2006). A Danish study that followed more than 4,800 patients with newly diagnosed bipolar disorder over 10 years found that long-term treatment with lithium, but not with other psychopharmacological agents, was associated with a reduced risk of developing dementia (Kessing *et al.* 2010). A study that analyzed data from a national health insurance database in Taiwan concluded that lithium use was significantly related to a reduced risk of stroke in patients with bipolar disorder. The association between lithium use and reduced stroke risk was strongest for patients who received the highest lithium dosages, experienced the longest durations of lithium treatment, and had the highest rates of lithium exposure (Lan *et al.* 2015).

Pregnant or Lactating Women and Their Children

The risks of lithium treatment during pregnancy and lactation must be carefully weighed against the risks of untreated bipolar disorder. It was once thought that pregnancy may provide a protective effect for new or worsening bipolar disorder; however, a longitudinal study of 89 women with bipolar disorder conducted by Viguera *et al.* (2007b) reported an overall recurrence risk of 71% during pregnancy, with the risk of recurrence two times greater among women who discontinued mood stabilizer treatment compared with those who did not. Those who discontinued the mood stabilizer also spent a larger percentage of their pregnancy ill (43%) compared with those who continued (9%). This is important because women with undertreated or untreated bipolar disorder

are thought to be at increased risk for perinatal complications and poor pregnancy outcomes (Jablensky *et al.* 2005; Lee and Lin 2010; Poels *et al.* 2018).

Although it is not generally thought that pregnancy elevates the relapse risk of bipolar episodes, the postpartum period, especially the first 3 months, is a particularly vulnerable time for relapse (Viguera *et al.* 2000; Wesseloo *et al.* 2016). A meta-analysis conducted by Wesseloo *et al.* (2016) found that the overall risk of postpartum relapse was 37% in women with a history of bipolar disorder. Women who continued medications during pregnancy were significantly less likely to experience a relapse in the postpartum period (23%) than those who discontinued medications (66%). Similarly, those who used mood-stabilizing medications during the postpartum period were also at lower risk of relapse (29%) than those who did not (65%). This high risk of recurrence has prompted experts in the field to recommend postpartum prophylactic treatment with a mood stabilizer for women with bipolar disorder (Wesseloo *et al.* 2016). It is important to highlight that lithium was the primary mood stabilizer used in the studies, leading the authors of the meta-analysis to emphasize that prophylactic lithium reduces the risk of bipolar recurrence during pregnancy and the postpartum period (Wesseloo *et al.* 2016).

Although prophylactic use of lithium during pregnancy may confer a lower risk of mood episode recurrence when compared with other mood stabilizers, it is not without other risks (Viguera *et al.* 2007a). Lithium freely crosses the placenta barrier, with maternal and fetal levels equilibrating (Newport *et al.* 2005). Several studies suggest that lithium exposure during pregnancy may elevate the risk of miscarriage, especially with first trimester exposure (Diav-Citrin *et al.* 2014; Fornaro *et al.* 2020; Poels *et al.* 2020). Newport *et al.* (2005) reported that lithium-exposed neonates were more likely than nonexposed neonates to be born preterm, to have lower birthweights, and to have longer hospital stays. However, a more recent meta-analysis of six international cohort studies concluded that lithium use during pregnancy did not elevate the risk of preterm birth, low birthweight, or small size for gestational age but was associated with a higher risk for admission to a neonatal special care unit compared with the mood disorder reference group (Munk-Olsen *et al.* 2018). In the same meta-analysis, lithium did not elevate the risk of preeclampsia, gestational diabetes, cesarean section, or postpartum hemorrhage.

Regarding teratogenic risk, data suggest that lithium exposure during pregnancy is less harmful than experts previously believed (Cohen *et al.* 1994). In fact, although the overall risk of Ebstein's anomaly--a rare cardiac malformation with an incidence of 1 in 20,000 live births--may be higher with lithium use (relative risk of 10-20 times that in the general population) than without, the absolute risk associated with first-trimester lithium exposure is thought to be 0.05%-0.1% (Cohen and Rosenbaum 1998). Three more recent investigations (Fornaro *et al.* 2020; Munk-Olsen *et al.* 2018; Patorno *et al.* 2017) reported higher rates of major malformations with lithium exposure when compared with the unexposed groups, but only two reported higher rates of cardiac malformations with first trimester lithium exposure (Fornaro *et al.* 2020; Patorno *et al.* 2017). Overall, lithium is not a high-risk teratogen, and the risk of cardiovascular anomalies with lithium is substantially lower than the risk of neural tube defects associated with some anticonvulsants used for mood stabilization.

Lithium exposure has been associated with neonatal adverse effects, such as hypoglycemia, nephrogenic diabetes insipidus, thyroid dysfunction, and neonatal lithium

toxicity (Poels *et al.* 2018). In the previously discussed study conducted by Newport *et al.* (2005), birth complications were directly correlated with higher placental lithium concentrations (> 0.64 mEq/L). In contrast, a more recent retrospective observational study did not find this correlation (Molenaar *et al.* 2021). Some experts recommend a dosage reduction or a brief suspension (24-48 hours) of lithium therapy before delivery to minimize neonatal complications (Graham *et al.* 2018; Molenaar *et al.* 2021; Newport *et al.* 2005). However, there is a lack of evidence supporting this practice. In contrast, other experts cite concern for elevated postpartum decompensation with lithium dosage reductions and instead recommend vigilant monitoring of lithium levels during labor and the first 2 weeks postpartum (Molenaar *et al.* 2021; Wesseloo *et al.* 2017).

Lithium is secreted in breast milk and is passed on to the infant in clinically significant levels (relative infant dose of 10% or greater). In a study of 10 mother-infant pairs, serum lithium levels in the infants ranged from 0.09 to 0.3 mEq/L (mean 0.16 mEq/L). Transient elevations in infant thyroid-stimulating hormone, blood urea nitrogen, and creatinine levels were observed without evident long-term effects (Viguera *et al.* 2007a). The study authors concluded that breastfeeding in the context of lithium therapy may be considered reasonable for a healthy infant when the mother's bipolar disorder is clinically stable, lithium monotherapy or a simple medication regimen is being used, and the pediatrician is supportive of the mother's breastfeeding while she is being treated with lithium. The American Academy of Pediatrics no longer considers the use of lithium a contraindication to breastfeeding and currently recommends that in addition to receiving counseling about the benefits of breastfeeding, parents be informed of the potential risks for infants exposed to clinically significant lithium levels and cautioned that the long-term effects of this exposure are unknown (Sachs and Committee on Drugs 2013).

Side Effects and Toxicology

Laboratory Monitoring

Before lithium therapy is started, a medical history should be obtained, as well as baseline renal laboratory tests (blood urea nitrogen, creatinine level, estimated glomerular filtration rate), thyroid function tests, a pregnancy test for women of childbearing age, and an electrocardiogram (ECG) for individuals older than 40 years (American Psychiatric Association 2002; McKnight *et al.* 2012; Yatham *et al.* 2018). The American Psychiatric Association practice guideline for the treatment of bipolar disorder suggests that renal function should be assessed every 2-3 months and thyroid function should be tested once or twice during the first 6 months of treatment. After the first 6 months, renal laboratory tests, thyroid function tests, and calcium should be monitored every 6-12 months or as clinically indicated (American Psychiatric Association 2002; McKnight *et al.* 2012; Shine *et al.* 2015; Yatham *et al.* 2018). Additionally, it is recommended that the lithium serum concentration be measured 5 days after the most recent dosage titration and then every 3-6 months or more frequently as clinically indicated (Yatham *et al.* 2018). Levels should be drawn approximately 12 hours after the last dose regardless of formulation (Yatham *et al.* 2018).

Central Nervous System

Cognitive Side Effects

Cognitive side effects have been reported to be among the more disturbing side effects experienced by patients receiving lithium maintenance treatment and are associated with self-reported nonadherence (Gitlin *et al.* 1989; Johnson *et al.* 2007). Patients may report feeling cognitively "dull." Although they are commonly reported, it is often challenging to determine whether the cognitive changes are due to the lithium itself, the general nature of bipolar disorder, residual symptoms, or the presence of comorbid psychiatric or medical conditions (Paterson and Parker 2017). Although research on the impact of lithium on several different cognitive domains, such as executive functioning and memory, has resulted in inconclusive findings, lithium does not appear to affect attention (Paterson and Parker 2017; Sabater *et al.* 2016). In fact, one study suggests that lithium may improve neurocognitive functioning (Burdick *et al.* 2020). In addition, data supporting the potential neuroprotective effects of lithium are growing. Long-term lithium treatment has been associated with elevated hippocampal volumes (Pfennig *et al.* 2014). This finding might explain how lithium may preserve memory and learning (Sabater *et al.* 2016).

Neurotoxicity

Neurotoxicity, delirium, and encephalopathy have been reported with lithium use. Specific populations with underlying neurological vulnerability have been noted to be at higher risk. Also, certain circumstances, such as concomitant electroconvulsive therapy or use of other psychotropics--especially first-generation antipsychotics--have been found to increase the risk of neurotoxic adverse effects from lithium treatment.

Neurotoxic reactions are potentially irreversible. Permanent neurological deficits reported after episodes of lithium intoxication (Apte and Langston 1983; Donaldson and Cuningham 1983) have included deficits in recent memory, ataxia, and movement disorders. Early hemodialysis may help prevent permanent sequelae in these cases. Donaldson and Cuningham (1983) also reported persistent neurological sequelae of lithium toxicity involving multiple sites within the nervous system. In a case series of 90 patients, Adityanjee *et al.* (2005) reported that the most common sequela in the syndrome of irreversible lithium-effectuated neurotoxicity was cerebellar dysfunction. The other typical neurological signs of this syndrome include extrapyramidal symptoms, brain stem dysfunction, and dementia (Ivkovic and Stern 2014).

Himmelhoch *et al.* (1980) found a greater incidence of lithium-induced neurotoxicity in older adults. Other risk factors include longer duration of exposure to higher lithium levels and presence of medical comorbidities, including nephrogenic diabetes insipidus, abnormal thyroid function and impaired renal function, preexisting neurological disease, and drug combinations including antipsychotics (Ivkovic and Stern 2014; Netto and Phutane 2012; Oakley *et al.* 2001).

Tremor

Postural tremor is one of the most commonly reported lithium side effects, with an estimated incidence of approximately 25% (reported range between 4% to 65%) (Gelenberg and Jefferson 1996). It generally appears early in treatment but may appear at any time. It is typically symmetrical and indistinguishable from an essential tremor. A severe or coarse tremor may indicate toxicity. Lithium-induced tremor can be managed by maintaining lithium levels at the lower end of the therapeutic range or by reducing or eliminating additive factors, such as caffeine intake. If lowering the dosage is not possible or is ineffective, an antidote, such as a beta-blocker, may be helpful in managing a debilitating tremor (Baek *et al.* 2014).

Metabolic Abnormalities

Thyroid Abnormalities

Lithium has been associated with the development of goiter, hypothyroidism, and, more rarely, hyperthyroidism (Czarnywojtek *et al.* 2020). In a chart review of 135 patients who underwent maintenance treatment with lithium, 38% had abnormal values on thyroid function tests (thyroid-stimulating hormone or free thyroxine index), with an association between laboratory abnormalities and length of time on lithium (Fagiolini *et al.* 2006). In a systematic review and meta-analysis, McKnight *et al.* (2012) reported that in comparison with placebo-treated subjects, lithium-treated patients had a sixfold higher risk of clinical hypothyroidism and showed higher levels of thyroid-stimulating hormone. In a retrospective study of 209 individuals who received lithium, Kirov (1998) found that 14.9% of the female patients and 3.4% of the male patients developed hypothyroidism. Reports have suggested that subclinical hypothyroidism during lithium therapy is even more common (Kleiner *et al.* 1999; Lombardi *et al.* 1993).

Lithium-induced hypothyroidism (LIT) can appear early in treatment but is generally associated with chronic use, with an average lithium treatment duration of 18 months before a hypothyroidism diagnosis (Kibirige *et al.* 2013). Risk factors for LIT include the presence of antithyroid antibodies (Bocchetta *et al.* 2007), female gender (Kirov 1998; Shine *et al.* 2015), age greater than 50 (Kirov 1998; Shine *et al.* 2015), and family history of hypothyroidism (Kusalic and Engelsmann 1999). Development of LIT does not necessitate lithium discontinuation and can be addressed by initiating thyroid supplementation. Although the reversibility of LIT is not well established, a recent retrospective cohort study by Lieber *et al.* (2020) reported successful discontinuation of the thyroid replacement after lithium discontinuation in 29 of 35 patients, suggesting it may be reversible for some patients.

Parathyroid Abnormalities

Chronic lithium exposure has been associated with hypercalcemia and hyperparathyroidism (Mifsud *et al.* 2020). Although reported prevalence rates vary, it is estimated that approximately one-quarter of lithium-treated patients experience hypercalcemia while taking lithium (Meehan *et al.* 2018). A meta-analysis by McKnight *et al.* (2012) found that lithium-treated patients demonstrated a 10% absolute risk of developing lithium-induced hyperparathyroidism, compared to 0.1% of the general population. Similar increases in parathyroid hormone (Albert *et al.* 2013) and calcium (Albert *et al.* 2013; Hayes *et al.* 2016; Shine *et al.* 2015) in lithium-treated patients have been reported in other studies as well. Monitoring of calcium levels at baseline and yearly, or more frequently in the presence of clinical symptoms, is suggested (McKnight *et al.* 2012; Shine *et al.* 2015).

Weight Gain

Weight gain is a commonly reported side effect of lithium. In one double-blind trial, the average weight change over 1 year was 4.2 kg (Calabrese *et al.* 2003). Along with lithium's cognitive side effects, weight gain is often cited by patients as a reason for treatment nonadherence (Gitlin *et al.* 1989; Johnson *et al.* 2007). Lithium has been associated with clinically significant weight gain (> 7%) (McKnight *et al.* 2012), which may pose a greater risk for patients who are obese before commencement of lithium treatment compared with those who are at normal weight (Bowden *et al.* 2006).

Renal Complications

Lithium has multiple renal effects, including those that occur early in treatment and those that occur with chronic use. Lithium can induce tubular dysfunction early in treatment, with reduced urinary concentrating capacity developing over the first 8 weeks of treatment. Nephrogenic diabetes insipidus occurs in 20%-87% of patients on lithium (Azab *et al.* 2015; Markowitz *et al.* 2000; Stone 1999). These effects may be partially mediated by lithium's action on water and sodium channels in the kidney (Grunfeld and Rossier 2009); thus, there has been renewed interest in using amiloride, a sodium channel-blocking diuretic, in an attempt to modify lithium's toxicity (Azab *et al.* 2015; Bedford *et al.* 2008).

Another important renal effect of lithium is chronic kidney disease, which tends to occur after 10-20 years of lithium treatment (Presne *et al.* 2003) at an estimated prevalence of 1.2% (Bendz *et al.* 2010) to 21% (Lepkifker *et al.* 2004), depending on the definition of renal insufficiency used. However, the risk of progressing to end-stage renal disease is small (0.5%-1%) (Bendz *et al.* 2010; Tredget *et al.* 2010). The clearest risk factors are duration of lithium use (Bendz *et al.* 2010; Bocchetta *et al.* 2015; Castro *et al.* 2016; Presne *et al.* 2003), dosing of lithium more than once a day (Castro *et al.* 2016), and higher serum lithium levels (Castro *et al.* 2016; Shine *et al.* 2015); additional possible risk factors are older age (Bendz *et al.* 2010; Bocchetta *et al.* 2015; Castro *et al.* 2016; Close *et al.* 2014; Presne *et al.* 2003), female sex (Castro *et al.* 2016; Shine *et al.* 2015), previous episodes of lithium toxicity, and presence of comorbid disorders (Castro *et al.* 2016; Lepkifker *et al.* 2004). The potential for chronic renal disease is the reason that close laboratory monitoring is required for patients on long-term lithium treatment (Shine *et al.* 2015). Once-daily dosing and maintaining low lithium levels when possible may be helpful in preventing long-term renal damage (Castro *et al.* 2016; Malhi and Tanious 2011). The decision of whether to stop lithium in the setting of renal impairment must be made collaboratively by the patient, the psychiatrist, and the nephrologist. Chronic kidney disease can progress to renal failure even after lithium is stopped; however, with mild or moderate renal dysfunction, there may be improvement if a change is made (Grunfeld and Rossier 2009).

Cardiac Changes

Lithium has been associated with a wide range of cardiac effects, ranging from benign electrocardiographic changes to fatal arrhythmias. Lithium intoxication (levels > 1.5 mEq/L) has been reported to cause cardiac alterations, including sinus bradycardia, sinus node dysfunction, and QTc prolongation (Mehta and Vannozzi 2017; Steckler 1994). T-wave changes, as well as ventricular irritability, may occur with lithium treatment

(Altinbas *et al.* 2014; Mitchell and Mackenzie 1982). T-wave depression (flattening, rounding, notching, and inversion) is the most commonly reported ECG change during chronic lithium therapy (Mehta and Vannozzi 2017). Chronic lithium use has also been associated with atrioventricular block (Martin and Piascik 1985) and sinus node dysfunction (Rosenqvist *et al.* 1993). Additionally, a Brugada pattern ECG (J point elevation, coved ST segment, and T-wave inversion) has been reported with lithium use, with an incidence of approximately 0.5% (Darbar *et al.* 2005; Yap *et al.* 2009). Although lithium does not appear to have a direct effect on blood pressure, elevated systolic blood pressure has been associated with lithium-induced ECG changes (Chen *et al.* 2020). Because of the potential risk of cardiac effects, careful monitoring of the pulse and electrocardiographic monitoring are recommended for patients older than 40 years and those with underlying cardiac disease (Chen *et al.* 2020; Roose *et al.* 1979; Tilkian *et al.* 1976).

Cutaneous Changes

Lithium is associated with a variety of cutaneous conditions, most frequently acne and psoriasis but also eczema, hair loss, hidradenitis suppurativa, nail dystrophy, and mucosal lesions. Prevalence estimates for adverse cutaneous effects in lithium-treated patients are as high as 45%. Most cases can be managed without lithium discontinuation; however, these adverse effects can be distressing to patients and may affect medication compliance (Yeung and Chan 2004).

Drug-Drug Interactions

Lithium With Other Mood Stabilizers

Lithium With Anticonvulsants

Lithium is commonly used in combination with other mood stabilizers, and although such combinations can be synergistic, polypharmacy may increase the risk of adverse reactions (Freeman and Stoll 1998; Lenox *et al.* 1996). The combination of lithium and valproate is often used in refractory mania. Interactions may include additive side effects, such as sedation, tremor, or weight gain, but the pharmacokinetics of lithium are not altered by the addition of valproate (Granneman *et al.* 1996). Lithium and carbamazepine have been combined for bipolar disorder refractory to lithium alone, but this combination may increase the risk of neurotoxicity (Chaudhry and Waters 1983; Kishimoto 1992; Shukla *et al.* 1984, 1985; Small *et al.* 1995). There are inconsistent reports about interactions between lithium and lamotrigine; whereas Chen *et al.* (2000) found no significant alterations in the pharmacokinetics of lithium in 20 healthy volunteers, another study showed that cotreatment with lithium may lower the serum concentration of lamotrigine (Reimers *et al.* 2005). Topiramate (Bialer *et al.* 2004), gabapentin (Frye *et al.* 1998; Vollmer *et al.* 1986), and benzodiazepines (Adler 1986; Modell *et al.* 1985; Sachs *et al.* 1990a, 1990b) exhibit no pharmacokinetic interactions with lithium.

Lithium With Antipsychotics

Although many investigators have reported safe and efficacious results from the concomitant use of lithium and antipsychotics for the treatment of bipolar disorder, the combination has been associated with increased risk of acute and irreversible neurotoxicity (including delirium, neuroleptic malignant syndrome, acute dyskinesias, and tardive dyskinesia) (Blake *et al.* 1992; Chen and Cardasis 1996; Cohen and Cohen 1974; de Leon and Spina 2018; Netto *et al.* 2019). Considering that lithium and antipsychotics are commonly prescribed together without incident, neurotoxicity is probably a rare phenomenon. Prospective data suggest that lithium can be combined with antipsychotics for acute mania without expected impact on the pharmacokinetics of either drug (Boulton *et al.* 2012; Bowden *et al.* 2010b; Chiu *et al.* 2014; Madhusoodanan *et al.* 2000; Szegedi *et al.* 2012). On the other hand, the use of clozapine with lithium should be done cautiously because the combination has been associated with CNS abnormalities including myoclonus, seizures, and electroencephalographic abnormalities (Kitagawa *et al.* 2021).

Lithium With Antidepressants

Lithium is often used concomitantly with antidepressants in the treatment of bipolar depression and refractory unipolar depression. In general, antidepressants are not thought to affect lithium pharmacokinetics (Sitsen *et al.* 2000; Troy *et al.* 1996). However, serotonin syndrome--a constellation of mental status and behavioral changes (either agitation or sedation), motor symptoms (restlessness, weakness, hyperreflexia, or ataxia), and autonomic dysfunction (nausea or vomiting, dizziness, sweating, fever)--has been reported with the use of lithium and serotonergic antidepressants (Adan-Manes *et al.* 2006; Fagiolini *et al.* 2001; Shahani 2012). In contrast, a retrospective study conducted by Bauer *et al.* (1996) found no increase in serotonergic adverse effects. Similarly, in an extensive review of systematic reports, Hawley *et al.* (2000) were unable to identify serious or lethal toxicities with the combined use of SSRIs and lithium.

Lithium With Nonpsychotropic Medications

NSAIDs, including cyclooxygenase 2 inhibitors, increase the risk of lithium toxicity by decreasing lithium clearance (Grandjean and Aubry 2009; Phelan *et al.* 2003). Because of the unpredictability of this interaction, it is generally best to advise patients on lithium to avoid NSAIDs, if possible. Although high-dose NSAID use has been associated with acute kidney injury in older adults and long-term NSAID use has been associated with the development of chronic kidney disease (Zhang *et al.* 2017), it is unclear whether the combination of lithium and an NSAID puts patients at an elevated risk of developing acute kidney injury or chronic kidney disease. Regardless, when lithium is used concurrently with NSAIDs, signs and symptoms of toxicity, lithium levels, and renal function should be monitored more diligently.

Because lithium excretion relies on renal clearance, diuretic medications may affect lithium levels, depending on their site of action. Thiazide diuretics trigger a compensatory increase in reabsorption in the proximal tubule and lead to elevations in lithium levels, whereas loop diuretics do not promote lithium reabsorption and do not greatly affect lithium levels (Finley *et al.* 1995). Osmotic diuretics increase lithium excretion and may counteract lithium toxicity, and either no change or a slight increase in lithium levels has been reported with potassium-sparing diuretics.

Neurotoxic and other adverse reactions have been associated with the concomitant administration of lithium with calcium channel blockers (Dubovsky *et al.* 1987; Finley *et al.* 1995; Wright and Jarrett 1991). Angiotensin converting enzyme inhibitors or angiotensin receptor 1 blockers may raise lithium levels (Finley *et al.* 1996). Serum lithium levels may increase in the context of sodium restriction (Bennett 1997). Lactulose may result in lithium toxicity, possibly by volume depletion, as reported in a case series (Bregman *et al.* 2014). On the other hand, theophylline and caffeine can decrease lithium concentrations (Cook *et al.* 1985). Importantly, if either is discontinued, lithium clearance may decrease, resulting in an increase in lithium concentration (Jefferson 1988).

Conclusion

Lithium is an important option in the evidence-based rational treatment of bipolar disorder. Bipolar disorder affects between 1% and 5% of the population (Akiskal *et al.* 2000) and causes significant morbidity and mortality, and the diagnosis of bipolar disorder carries a high risk for suicide. A summary published in 1990 estimated that 25%-50% of individuals with bipolar disorder attempt suicide and 19% complete suicide (Goodwin *et al.* 2007).

Lithium has been shown to be effective for acute mania and bipolar depression and as a prophylactic treatment for bipolar disorder. Some data suggest that conditions such as comorbid neurological illness and mixed episodes may be indicators of illness that is more responsive to mood stabilizers other than lithium. Evidence also suggests that lithium can play a role in the treatment of refractory unipolar depression for patients at risk for suicide. Lithium may be less risky than anticonvulsants in pregnancy. However, a 20-year trend in pharmacological choice in bipolar disorder in the outpatient setting in a nationally representative dataset shows an approximately 13% decrease in lithium use and an increase of approximately 39% in second-generation antipsychotic use (Rhee *et al.* 2020). Although we continually seek new treatments and hope that they will be more efficacious and better tolerated than older medications, lithium remains a strong first-line treatment option despite being discovered over 70 years ago, the only example of such longevity in psychiatry.

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CHAPTER 38

Valproate

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History and Discovery

Valproate was the first mood stabilizer to be studied as an alternative to lithium (Lambert *et al.* 1966). An enteric-coated formulation, divalproex sodium, was approved in the United States for the treatment of mania in 1995. An extended-release (ER) formulation of divalproex was approved for migraine in 2001 and for mania in 2006. Valproate, both as divalproex and as other formulations, is now approved worldwide for the treatment of mania. Valproate sodium injection is an antiepileptic drug indicated as an intravenous alternative for patients in whom oral administration of valproate products is temporarily not feasible (Hospira 2013).

Pharmacological Profile

Valproic acid (dipropylacetic acid) (Figure 38-1 is an eight-carbon branched-chain carboxylic acid that is structurally distinct from other antiepileptic and psychotropic compounds (Bocci and Beretta 1976; Levy 1984). Its three-dimensional structure overlays that of naturally occurring fatty acids (e.g., oleic and linolenic acids). Valproate binds in a saturable manner to the neuronal membrane sites to which these longer-chain fatty acids attach. Some of valproate's molecular mechanisms are probably a consequence of this physiochemical property.

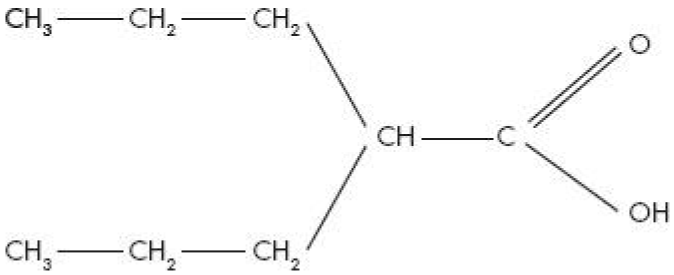

FIGURE 38-1. Chemical structure of valproic acid.

Pharmacokinetics and Disposition

Valproate is commercially available in the United States in five oral preparations: divalproex sodium (an enteric-coated, stable-coordination compound containing equal proportions of valproic acid and valproate sodium in a 1:1 molar ratio) delayed-release tablet (AbbVie Inc. 2023a); valproic acid capsule and syrup (Abbott Laboratories 2009); valproate sodium injection (Hospira 2013); divalproex sodium sprinkle capsule (containing coated particles of divalproex sodium), which can be ingested intact or pulled apart for contents to be sprinkled on food (AbbVie Inc. 2023c); and a divalproex sodium ER tablet that provides once-daily dosing and a substantially flatter peak-to-trough ratio (AbbVie Inc. 2023b) (Table 38-1). Sodium valproate for intravenous injection has been demonstrated to provide a reduction in manic symptoms within 1 day or less (Grunze *et al.* 1999). In addition, valproate sodium can be compounded in suppository form for rectal administration, and diluted valproate sodium solution can also be administered rectally. The valproate ion is the common compound in plasma.

TABLE 38-1. Valproic acid dosage forms

Active ingredient	Dosage form/ route of administration	Strength/therapeutic equivalence
Divalproex sodium		
	Capsule, delayed-release pellets; oral	Eq 125 mg valproic acid
	Tablet, delayed release; oral	Eq 125 mg valproic acid
	Tablet, delayed release; oral	Eq 250 mg valproic acid
	Tablet, delayed release; oral	Eq 500 mg valproic acid
	Tablet, extended release; oral	Eq 250 mg valproic acid
	Tablet, extended release; oral	Eq 500 mg valproic acid
Valproic acid		
	Capsule; oral	250 mg
	Syrup; oral	250 mg/5 mL
Valproate sodium		
	Injectable; injection	Eq 100 mg base/mL

Source. Data from U.S. Food and Drug Administration 2023.

The bioavailability of valproate approaches 100% with all preparations (Wilder 1992). With the exception of divalproex sodium, all preparations taken orally are rapidly absorbed. Sodium valproate and valproic acid attain peak serum concentrations within 2 hours. Divalproex sodium reaches peak serum concentrations in 3-8 hours (AbbVie Inc. 2023a). In comparison with the delayed-release tablets, the ER form of divalproex sodium has an earlier onset of absorption and an approximately 20% smaller difference between trough and peak serum levels (AbbVie Inc. 2023b) (Figure 38-2).

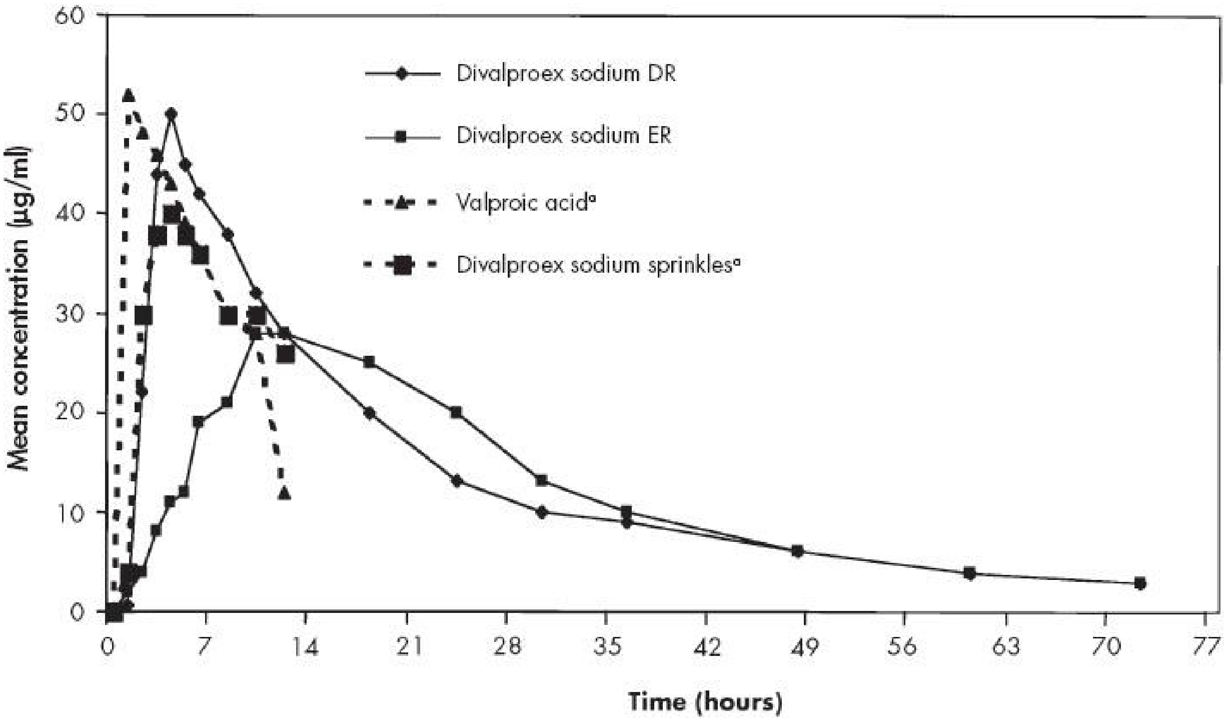

FIGURE 38-2. Mean plasma valproate concentrations with different formulations.

DR = delayed-release; ER = extended-release.

[a]Data derived from different studies after 500-mg doses.

Source. Abbott Laboratories, data on file.

Valproate is highly protein bound, predominantly to serum albumin and proportional to the albumin concentration. Although patients with low levels of albumin have a higher fraction of unbound drug, the steady-state level of total drug is not altered. Only the unbound drug crosses the blood-brain barrier and is bioactive. Thus, when valproate is displaced from protein-binding sites through drug interactions, the total drug concentration may not change; however, the pharmacologically active unbound drug does increase and may produce signs and symptoms of toxicity. Moreover, when the plasma concentration of valproate rises in response to dosage increases, the amount of unbound (active) valproate increases disproportionately and is metabolized, with an apparent increase in clearance of total drug, yielding lower-than-expected total plasma concentrations (Levy 1984; Wilder 1992) (Figure 38-3). In addition, protein binding of valproate is increased by low-fat diets and decreased by high-fat diets. Because of lower serum protein levels, women and older adults generally have a higher proportion of the active free moiety.

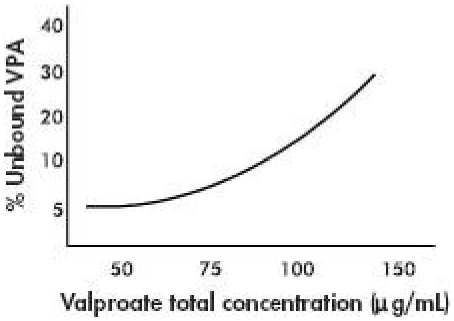

FIGURE 38-3. Total valproate (VPA) concentrations in the presence of dosage increases.

As the total concentration of valproate increases, protein-binding sites become saturated, and the percentage of unbound to bound valproate increases.

Source. Adapted from Figure 4 (p. 66S) in Wilder BJ: "Pharmacokinetics of Valproate and Carbamazepine." *Journal of Clinical Psychopharmacology* 12(1 Suppl):64S-68S, 1992. Copyright (c) 1992, Williams & Wilkins. Used with permission.

The concentration range needed for good clinical effect in mania is approximately 45-125 mg/mL (Bowden *et al.* 1996). Patients who are able to tolerate higher serum levels--up to about 125 mg/mL--may experience greater improvement (Allen *et al.* 2006). Patients with rapid cycling in the context of bipolar II disorder or cyclothymic disorder may respond to serum valproate concentrations of less than 50 mg/mL (Jacobsen 1993). In maintenance treatment, patients whose serum valproate levels were maintained between 75 mg/mL and 99 mg/mL had superior outcomes compared with patients whose serum levels were either lower or higher than this range (Keck *et al.* 2005). Valproate is metabolized in the liver, primarily through glucuronidation.

When used for the treatment of bipolar disorder, valproate is usually begun at a dosage of 15-20 mg/kg/day. The drug can be orally loaded at 20-30 mg/kg/day for patients with acute mania to induce a more rapid response (Hirschfeld *et al.* 2003). The dosage of valproate is increased according to the patient's response and tolerance of side effects, usually by 250-500 mg/day every 1-3 days, to serum concentrations of 45-125 mg/mL. Of note, sedation, increased appetite, and reductions in white blood cell counts and platelet counts all become more common at serum concentrations greater than 100 mg/mL (Bowden *et al.* 2000).

Mechanism of Action

Valproate stimulates extracellular signal-regulated kinase and indirectly inhibits glycogen synthase kinase 3 (Cournoyer and Desrosiers 2009). Valproate also stimulates the activity of Bcl-2, a neuroprotective substance (Gray *et al.* 2003). Valproate inhibits histone deacetylase, and many of the drug's subcellular effects (e.g., increasing brain-derived neurotrophic factor) are probably a consequence of this action (Harwood and Agam 2003; Perova *et al.* 2010).

Indications and Efficacy

Acute Mania in Bipolar Disorder

Valproate is an effective treatment for acute mania in adults. Its efficacy in this population is slightly less than that of olanzapine and indistinguishable from that of lithium (Bowden 2011; Marcus *et al.* 2011; Muller-Oerlinghausen *et al.* 2000; Tohen *et al.* 2002; Yatham *et al.* 2003). Valproate has been studied in adjunctive regimens with various antipsychotics, with findings consistently pointing to greater efficacy for combination treatment than for monotherapy (Bowden 2011; Marcus *et al.* 2011; Muller-Oerlinghausen *et al.* 2000; Tohen *et al.* 2002; Yatham *et al.* 2003).

Valproate has been studied in combination with an atypical antipsychotic in patients with an inadequate response to lithium or valproate monotherapy (Tohen *et al.* 2002). The combination was more effective than monotherapy plus placebo. In a similar study, adding either risperidone or haloperidol for patients inadequately responding to valproate monotherapy was more effective than monotherapy plus placebo (Sachs *et al.* 2002). These findings suggest that adding an antipsychotic to the treatment of patients inadequately responding to valproate monotherapy is effective.

Few studies of any antimanic agent have addressed its effectiveness in hypomanic episodes, which are more common than manic episodes, even in patients with bipolar I disorder. In an 8-week randomized, double-blind, placebo-controlled study of outpatients with bipolar and related disorders manifesting hypomanic symptoms, divalproex ER was significantly more effective than placebo in reducing hypomanic or mild manic symptoms ($P = 0.024$) (McElroy *et al.* 2010).

Acute Depression in Bipolar Disorder

Four small (total sample in all studies: 140) double-blind, placebo-controlled 8-week studies of divalproex have been conducted (Davis *et al.* 2005; Ghaemi *et al.* 2007; Muzina *et al.* 2011; Sachs *et al.* 2001). Three of the four studies reported positive results, and there was a trend favoring divalproex in the fourth (Sachs *et al.* 2001).

Maintenance Treatment of Bipolar Disorder

One large double-blind, placebo-controlled maintenance study of valproate monotherapy has been published (Bowden *et al.* 2000). Patients who recovered with open treatment with either divalproex or lithium, had satisfactory lithium or valproate blood levels, and were in remission for at least 2 weeks were randomly assigned to maintenance treatment with divalproex, lithium, or placebo. Neither the divalproex group nor the lithium group differed significantly from the placebo group on time to any mood episode. The rate of relapse to mania with placebo was lower than anticipated. Among the subset of patients who received divalproex in the open acute phase, those randomly assigned to continue on divalproex in the double-blind maintenance phase had significantly longer times to recurrence of any mood episode or a depressive episode (Bowden *et al.* 2000).

Maintenance studies of combination treatment with quetiapine were much more revealing of efficacy. Two studies with identical designs (Suppes *et al.* 2009; Vieta *et al.* 2008) enrolled patients with bipolar disorder and either a depressed or a manic episode who had been successfully treated with a combination of quetiapine and either lithium or divalproex and who had been in remission for at least 12 weeks. Patients were randomly assigned to either continue on the quetiapine and lithium/divalproex combination or receive lithium/divalproex and a placebo and were followed for 2 years. The patients treated with lithium/divalproex and placebo were more than twice as likely as those receiving the combined treatment to relapse into either a manic or a depressive episode.

Mania Secondary to Head Trauma or Neurodevelopmental and Neurodegenerative Disorders

Evidence suggesting that secondary or complicated mania responds well to valproate is mixed. In an open study of 56 valproate-treated patients with mania, response was associated with the presence of nonparoxysmal abnormalities on the electroencephalogram but not with neurological soft signs or abnormalities on computed axial tomography scans of brain (McElroy *et al.* 1988). A study from the 1980s (Pope *et al.* 1988) suggested that manic patients who had experienced a closed-head injury before the onset of bipolar disorder were more likely to respond successfully to valproate treatment for mood symptoms.

Agitation and Clinical Decline in Older Adults With Dementia

Patients with dementia are often institutionalized for agitation and behavioral disturbances. In a randomized, blinded study in which 56 nursing home residents with agitation and dementia received either placebo or individualized doses of divalproex, the drug-placebo difference on Brief Psychiatric Rating Scale Agitation scores significantly favored divalproex. Side effects occurred in 68% of the divalproex group and 33% of the placebo group and were generally rated as mild (Porsteinsson *et al.* 2001). Six weeks of open continuation treatment resulted in further decreases in agitation. Divalproex serum levels were greater than 40 mg/mL in both the acute blinded phase and the open continuation phase (Porsteinsson *et al.* 2003). Patients with dementia should generally receive valproate dosages lower than 1,000 mg/day to ensure adequate tolerability (Profenno *et al.* 2005). A small randomized, placebo-controlled study of valproate in the treatment of aggression in dementia failed to find any difference between valproate and placebo, although the fixed dosage used (valproate 480 mg/day) may have been inadequate (Sival *et al.* 2002).

Valproate also was studied for its potential utility in preventing or delaying illness progression in 313 nursing home residents with moderate Alzheimer's disease who had not yet experienced agitation or psychosis. Time to emergence of clinically significant agitation or psychosis did not differ between the valproate and placebo groups, and valproate was associated with serious adverse effects in the patients (Tariot *et al.* 2011). Taken in the aggregate, these studies suggest that although valproate at low dosages can decrease dementia-related agitation in some patients, valproate has no utility in slowing or preventing disease progression in Alzheimer's dementia.

Irritability and Aggression

Valproate has been reported to be effective in reducing irritability and aggression among diverse patient populations, including patients with autism spectrum disorders or personality disorders. In a 12-week double-blind study of children and adolescents with autism spectrum disorders, irritability measures were significantly improved with divalproex compared with placebo. Overall, 62% of the divalproex-treated subjects and 9% of the placebo subjects (OR, 16.7) were responders (Hollander *et al.* 2010).

In a randomized, placebo-controlled, double-blind study, 249 patients with Cluster B personality disorders, intermittent explosive disorder, or posttraumatic stress disorder were treated for 12 weeks with either divalproex or placebo. Although divalproex did not separate from placebo in the combined analysis of all patient groups, aggression and irritability scores among the 96 Cluster B patients showed significant improvement over the course of the study (Hollander *et al.* 2003).

Cotherapy in Schizophrenia

In a 4-week randomized, double-blind study, 242 patients with schizophrenia were assigned to receive either monotherapy with an antipsychotic (risperidone or olanzapine) or adjunctive treatment with divalproex plus the antipsychotic drug. Compared with participants receiving monotherapy, those who received combination therapy showed significantly greater improvement on Positive and Negative Syndrome Scale-Total and Positive and Negative Syndrome Scale positive symptom subscale scores from day 3 through day 21 but not at day 28. Platelet counts decreased with combination therapy (Casey *et al.* 2003).

Bipolar Disorder With Comorbid Alcohol Use Disorder

Bipolar disorder is often associated with substance use disorders, particularly alcoholism. In a prospective, blinded, placebo-controlled study, 59 patients with bipolar I disorder and DSM-IV (American Psychiatric Association 1994) alcohol dependence were treated with lithium carbonate and psychosocial interventions for 24 weeks, with half randomly assigned to receive adjunctive valproate. The addition of valproate was associated with significantly fewer heavy drinking days, fewer drinks per heavy drinking day, and fewer drinks per drinking day. Higher serum valproate concentrations were correlated with improved alcohol use outcomes. Both manic and depressive symptoms improved equivalently (Salloum *et al.* 2005).

In a 12-week double-blind, placebo-controlled trial, divalproex treatment was associated with a significantly reduced rate of relapse to heavy drinking; however, no significant differences were found in other alcohol-related outcomes. Significantly greater decreases in irritability were found in the divalproex-treated group than in the placebo-treated group, but no significant between-group differences were seen on measures of impulsivity (Brady *et al.* 2002).

Mixed Mania as a Potential Predictor of Positive Response to Valproate Versus Lithium

Patients with mixed manic presentations experienced greater symptom improvement with divalproex than with lithium treatment in two randomized studies (Freeman *et al.* 1992; Swann *et al.* 1997), one of which (Swann *et al.* 1997) was placebo controlled (reviewed in Bowden 2003). Patients with mixed manic symptoms and patients with pure manic symptoms showed equivalent improvement with divalproex (Swann *et al.* 1997). By contrast, during maintenance treatment patients with mixed mania had equivalent responses to divalproex and lithium, with evidence of higher rates of adverse effects as a function of the illness features of mixed mania, compared with rates of adverse effects in patients with euphoric mania (Bowden *et al.* 2005; Singh *et al.* 2013). These results suggest that effective long-term management of mixed manic states may require medication regimens that are more complex than monotherapy (Bowden 1995).

Side Effects and Toxicology

Valproate has FDA-mandated black box warnings for hepatotoxicity, fetal risk (including major congenital malformations, particularly neural tube defects), and pancreatitis. These potential adverse effects are discussed in the appropriate sections that follow (Murru *et al.* 2015).

Gastrointestinal Effects

Common gastrointestinal effects of valproate include nausea, vomiting, diarrhea, dyspepsia, and anorexia. These effects are dose dependent, are usually encountered at the start of treatment, and are often transient (DeVane 2003). Immediate-release formulations of valproic acid are more likely than ER and enteric-coated formulations of divalproex sodium to cause adverse events (Horne and Cunanan 2003; Zarate *et al.* 1999).

Tremor

Tremor consequent to valproate use resembles benign essential tremor and may respond to a reduction in dosage. Use of the ER or enteric-coated formulation may lessen the frequency of tremor (Wilder 1992; Zarate *et al.* 1999). Beta blockers, such as propranolol, are often helpful in reducing tremor.

Sedation

Mild sedation is common at initiation of valproate treatment. This adverse effect is dosage dependent and may be minimized by dosage reduction, slower titration, use of ER formulations, or taking all medication at bedtime.

Pancreatitis

Idiosyncratic acute pancreatitis is a rare but serious adverse event associated with valproate. Pancreatitis may occur at any point during treatment. It manifests as abdominal pain, nausea, vomiting, or anorexia. If these symptoms occur, the patient should immediately discontinue the medication and alert the doctor.

Hematological Effects

Leukopenia and thrombocytopenia are directly related to higher valproate serum levels, usually 100 mg/mL or greater (Acharya and Bussel 1996; Bowden *et al.* 2000). Thrombocytopenia is usually mild and rarely associated with bleeding complications. Management consists of dosage reduction. Platelet counts below 75,000/mm^3 should be monitored and regularly reassessed, because counts lower than this level are more frequently associated with bruising or bleeding (Zarate *et al.* 1999).

Hepatotoxicity

The risk of liver toxicity from valproate is largely limited to individuals younger than 2 years, whose hepatic function is still immature (Tohen *et al.* 2003). These effects usually occur within the first 6 months of treatment. Concurrent administration of other anticonvulsants increases the risk. Hepatotoxicity may manifest as weakness, lethargy, facial edema, anorexia, vomiting, and seizures. Obtaining liver function measures at baseline and monitoring them frequently during the first 6 months of treatment is essential.

Divalproex sodium is contraindicated for patients with hereditary neurometabolic syndromes caused by mitochondrial DNA polymerase gamma gene mutations and related disorders (AbbVie Inc. 2023a)

Weight Gain

Weight gain of 1.36-10.9 kg is seen in 3%-20% of patients taking valproic acid for periods ranging from 3 to 12 months (Bowden 2003). Weight gain has been consistently less with valproate than with olanzapine in comparison studies (1.22 kg vs. 2.79 kg) (Tohen *et al.* 2003; Zajecka *et al.* 2002). Valproate serum levels greater than 125 mg/mL are more likely than lower levels to be associated with weight gain (Bowden 2000). If increased appetite and weight gain occur with valproate, the dosage should be lowered as long as clinical effectiveness is maintained; alternatively, valproate should be discontinued and replaced with a regimen without risk of weight gain.

Cognitive Effects

Valproate infrequently produces adverse effects on cognitive functioning, and, conversely, it improves cognition in some patients (Prevey *et al.* 1996).

In a 20-week randomized, observer-blinded, parallel-group investigation, the addition of valproate to carbamazepine resulted in improvement in short-term verbal memory (Aldenkamp *et al.* 2000). No adverse cognitive effects associated with use of valproate were seen in a group of older adults (mean age 77 years) (Craig and Tallis 1994).

Lipid Profile Effects

Several studies indicate that valproate significantly reduces total and low-density lipoprotein cholesterol levels and increases high-density lipoprotein cholesterol levels in long-term treatment (Geller *et al.* 2012), and that it may protect against the adverse effects of some antipsychotic drugs on lipid function (Bowden *et al.* 2000; Casey *et al.* 2003; Tohen *et al.* 2003). A 3-week study of valproate in mania indicated reductions in cholesterol, high-density lipoprotein, and low-density lipoprotein compared with placebo and reported the effect to be limited to subjects who had total cholesterol levels of 200 mg/dL or greater at study entry (Bowden *et al.* 2006).

Polycystic Ovary Syndrome

Women taking valproate have a slightly higher frequency of polycystic ovary syndrome (PCOS) compared with women taking with other medications (Bilo and Meo 2008). PCOS is characterized by hyperandrogenism, irregular menstruation, and obesity. Obesity may be a mechanistic pathway whereby valproate (and potentially other drugs) predisposes women to PCOS. It is advisable to treat weight gain as a risk factor for possible development of PCOS and to intervene as needed to avoid clinically significant weight gain (Bilo and Meo 2008).

Hair Loss

Hair loss may occur early in treatment and is usually transient. Frequency of hair loss may be greater in women than in men (Lajee and Parsonage 1980). Dosage reduction and separation of valproate dosing from meals can be helpful in controlling this effect; supplemental zinc and selenium ingestion via multivitamin tablets also may be useful.

Use During Pregnancy and Lactation

Teratogenic Effects

Valproate is associated with an increased incidence of birth defects, including neural tube defects, craniofacial anomalies, limb abnormalities, and cardiovascular anomalies, especially if exposure to valproic acid occurs in the first 10 weeks of gestation (Kinrys *et al.* 2003; Samren *et al.* 1997). Neural tube defects, the most serious of the congenital anomalies, occur in 1%-4% of such infants. The risk of malformations is increased with higher dosages and higher serum levels of valproate and with concomitant use of other anticonvulsants (Anmella *et al.* 2019).

Developmental Effects

Exposure to valproate in utero is associated with a high risk (up to 40%) of developing serious neurodevelopmental disorders in childhood. These disorders include cognitive impairments, growth restriction, and behavioral abnormalities.

Because of the increased risk of teratogenic and developmental effects, women of childbearing age should use valproate only in extreme circumstances. Some regulatory agencies have banned its use altogether in this population (Anmella *et al.* 2019).

Overdose

Recovery from overdose-induced coma has occurred with serum valproate concentrations greater than 2,000 mg/mL. In addition, serum valproate concentrations have been reduced by hemodialysis and hemoperfusion, and valproate-induced coma has been reversed with naloxone (Rimmer and Richens 1985).

Drug-Drug Interactions

Because valproate is highly protein bound and extensively metabolized by the liver, a number of potential interactions may occur with other protein-bound or extensively metabolized drugs (Fogel 1988; Rimmer and Richens 1985). Thus, free fraction concentrations of valproate in serum can be increased, and valproate toxicity can be precipitated, by coadministration of other highly protein-bound drugs (e.g., aspirin) that can displace valproate from its protein-binding sites.

In the context of coadministration, valproate's competitive inhibition of lamotrigine excretion via glucuronidation requires that lamotrigine be started at a lower dosage--usually 25 mg every other day--with increases implemented cautiously. Lamotrigine's steady-state plasma concentrations are also generally lower when the drug is used with valproate, although not in all patients.

Conclusion

Valproate's broad spectrum of efficacy in bipolar and related disorders and generally good tolerability make it an important treatment option for patients with bipolar disorder. For optimal results, most patients should be treated with the formulation that permits once-daily dosing and has the lowest peak-to-trough serum level, which in the United States currently is divalproex ER. Although onset of action of valproate occurs quickly with use of loading-dose strategies, gradual dosage titration is the preferred method of treatment initiation for most manic patients. Medication tolerability is of paramount importance in fostering patient adherence to long-term treatment regimens.

During maintenance treatment, it is often necessary to reduce the dosage if adverse effects occur. Valproate is principally effective in and prophylactic for manic symptoms, although its prophylactic benefits in depression have been demonstrated. A history of multiple affective episodes or a current presentation characterized by irritability may be a particularly strong indicator of a favorable response to valproate. Although some patients may achieve acute and sustained remission with valproate monotherapy, many patients are more effectively treated with combinations, including other mood stabilizers and adjunctive medications. All current medications with established or putative roles in bipolar disorder can be combined with valproate.

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CHAPTER 39

Carbamazepine, Oxcarbazepine, and Eslicarbazepine

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Pharmacotherapy of bipolar disorders is complex and rapidly evolving. Antipsychotics, antidepressants, anxiolytics, and new-generation anticonvulsants are commonly combined with traditional first-line mood stabilizers (lithium, valproate, carbamazepine) in clinical settings (American Psychiatric Association 2002; Ketter 2005; Suppes *et al.* 2005). Clinicians are challenged with integrating complex data regarding efficacy and adverse-effect profiles with pharmacological properties in their efforts to provide safe, effective, state-of-the-art pharmacotherapy for patients with bipolar disorder.

In this chapter, we review the pharmacology of carbamazepine and its analog oxcarbazepine. In the past, carbamazepine was considered an alternative to lithium and valproate rather than a first-line intervention in the treatment of bipolar disorder (American Psychiatric Association 2002), largely owing to methodological limitations of early studies of efficacy in bipolar disorder, complexity of use as a result of adverse effects and drug-drug interactions, and an initial lack of an FDA indication for the treatment of bipolar disorder. Carbamazepine received an FDA indication for the treatment of acute manic and mixed episodes in bipolar disorder following the publication of evidence from two randomized double-blind, placebo-controlled, parallel-group studies in patients with bipolar disorder (Weisler *et al.* 2004, 2005). Importantly, carbamazepine and oxcarbazepine may offer favorable efficacy and tolerability--in particular, less weight gain and fewer metabolic problems--for selected patients and thus can be important treatment alternatives (Akiskal *et al.* 2005). Likewise, the active monohydride metabolite of oxcarbazepine, licarbazepine, and its prodrug, the marketed product eslicarbazepine acetate, have good tolerability, although evidence of their efficacy in bipolar disorder is lacking.

History and Discovery

As one of the first alternatives to lithium and first-generation antipsychotics to become available, carbamazepine has played an important role in the development of therapeutic interventions for bipolar disorder (Post *et al.* 2007). Carbamazepine was developed in 1957 by J. R. Geigy AG in Europe, and its efficacy was established for epilepsy and paroxysmal pain by the 1960s and for bipolar disorder by the early 1970s (Takezaki and Hanaoka 1971). In the 1970s, acute mania was managed primarily with lithium and first-generation antipsychotics. Lithium was dramatically effective for patients with classical euphoric mania but was less effective for individuals with mixed or dysphoric mania, rapid cycling, a higher number of previous episodes, mood-incongruent delusions, or concurrent substance use disorders (Ketter and Wang 2002). Furthermore, starting treatment with lithium with a slow initial dosage titration meant that there was often a substantial delay before the medication's beneficial effects were experienced.

Limitations of lithium and first-generation antipsychotics led investigators to explore other treatment options for bipolar disorder. On the basis of early reports of favorable psychotropic profiles in patients with epilepsy and preliminary observations in subjects with mood disorders, systematic investigations of carbamazepine (Ballenger and Post 1978) and valproate commenced, and these anticonvulsants emerged as effective in acute mania. Carbamazepine and valproate were used off-label for bipolar disorder in the 1980s and early 1990s, respectively. The carbamazepine analog oxcarbazepine was anecdotally reported as useful in bipolar disorder in the 1980s (Muller and Stoll 1984), but it was not marketed in the United States for the treatment of epilepsy until 2000.

Because of economic concerns such as patent protection limitations and the high cost of obtaining FDA approval, a carbamazepine indication for bipolar disorder was not initially sought in the United States. A proprietary carbamazepine beaded extended-release capsule formulation (Equetro) received an FDA indication for the treatment of acute manic and mixed episodes in patients with bipolar disorder in late 2004.

Oxcarbazepine was approved for the treatment of epilepsy in the United States in 2000, following the development of several new anticonvulsants in the 1990s. Those anticonvulsants have heterogeneous psychotropic profiles (Ketter *et al.* 2003). Only the older drug phenytoin (Mishory *et al.* 2000) and oxcarbazepine (Emrich 1990) appear to be effective thus far in controlled (albeit small) trials in acute mania, and lamotrigine seems to be effective in acute and maintenance treatment of bipolar depression. FDA approval has not been sought for oxcarbazepine in the treatment of acute mania in the United States. On the basis of its greater ease of use, some clinicians consider oxcarbazepine to be an alternative to carbamazepine (American Psychiatric Association 2002). However, oxcarbazepine use remains limited by the lack of adequate data supporting its efficacy in bipolar disorder.

Licarbazepine, the active monohydroxy metabolite of oxcarbazepine, was initially assessed by Novartis Pharmaceuticals for treatment of acute mania rather than epilepsy. As of 2023, the results of three randomized controlled trials (on ClinicalTrials.gov) of licarbazepine in acute mania had not yet been published. In 2009, the European Medicines Agency approved eslicarbazepine acetate, a prodrug for the *S*-enantiomer of licarbazepine (Zebinix; BIAL-Portela), for the treatment of epilepsy. In 2013, the FDA approved eslicarbazepine acetate (Aptiom; submitted by Sunovion Pharmaceuticals under license from BIAL-Portela) for epilepsy. Although eslicarbazepine acetate may have greater tolerability than carbamazepine and does not carry black box warnings, its efficacy in acute mania has not been established (Grunze *et al.* 2015).

Structure-Activity Relationships

Carbamazepine is an iminostilbene derivative with a dibenzoazepine nucleus. It has a carbamyl (carboxamide) group at position 5 that seems to be associated with substantial anticonvulsant effects. Like imipramine, carbamazepine has a tricyclic structure. However, imipramine has a 5-aryl substituent, whereas carbamazepine has a 5-carboxamide substituent; this structural difference is thought to mediate carbamazepine's markedly different effects in comparison with imipramine, as described later in this chapter (see section "Mechanisms of Action"). Oxcarbazepine differs structurally from carbamazepine only in that it has a ketone substitution at the 10,11-position, and (as noted later) the bulk of the evidence thus far suggests that this structural similarity is paralleled by mechanistic similarity. Eslicarbazepine acetate, like oxcarbazepine, has a stabilizing subgroup at the 10,11-position (an acetoxy side chain) and is metabolized to the *S*-isomer of the common metabolite of oxcarbazepine, licarbazepine (Almeida and Soares-da-Silva 2007).

Pharmacological Profiles

Carbamazepine and oxcarbazepine have preclinical anticonvulsant profiles that are somewhat similar to that of phenytoin and less broad than that of valproate or lamotrigine. Like phenytoin, valproate, and lamotrigine, carbamazepine and oxcarbazepine are effective in the maximal electroshock model of generalized tonic and/or clonic seizures and in seizure blockade resulting from amygdala kindling (a model of partial seizures). Like phenytoin but unlike valproate and lamotrigine, carbamazepine and oxcarbazepine are not effective in the pentylenetetrazole model of absence seizures. In addition, like phenytoin and lamotrigine (but unlike valproate), carbamazepine and oxcarbazepine fail to block kindling development (a model of epileptogenesis).

As expected from their preclinical profiles, carbamazepine and oxcarbazepine--like phenytoin, valproate, and lamotrigine--are effective in partial seizures with and without secondary generalization. And like phenytoin but unlike valproate and lamotrigine, carbamazepine and oxcarbazepine are ineffective in absence seizures. Carbamazepine and oxcarbazepine also have analgesic effects in paroxysmal pain syndromes and thus are effective in trigeminal neuralgia.

Eslicarbazepine acetate, which shares a common active metabolite with oxcarbazepine, has a similar preclinical anticonvulsant profile. Thus, eslicarbazepine acetate, like oxcarbazepine, is effective in the maximal electroshock model of generalized tonic and/or clonic seizures and in blocking seizures resulting from amygdala kindling (Almeida and Soares-da-Silva 2007).

Pharmacokinetics and Disposition

Carbamazepine

Carbamazepine is available in the United States as a proprietary product (Tegretol; Novartis Pharmaceuticals 2015) supplied in suspension (100 mg/5 mL), chewable tablet (100 mg), immediate-release tablet (200 mg), and extended-release tablet (Tegretol XR 100, 200, and 400 mg) formulations. The additional proprietary formulation Carbatrol, an extended-release capsule, is marketed for epilepsy and is available in strengths of 100, 200, and 300 mg (Shire US 2013). The FDA has approved generic equivalent products for all of these dosage forms. Equetro (Validus Pharmaceuticals 2021), another extended-release capsule, is available in the same strengths as Carbatrol and is FDA approved and marketed for bipolar disorder (U.S.

Food and Drug Administration 2023). Intramuscular and depot formulations are not available.

Carbamazepine is extensively metabolized, with only about 3% being excreted unchanged in the urine. The main metabolic pathway of carbamazepine (to its active 10,11-epoxide, carbamazepine-E) seems to be primarily via cytochrome P450 (CYP) isozyme CYP3A3/4 (Figure 39-1, top), with a minor contribution by CYP2C8 (Kerr *et al.* 1994). This epoxide pathway accounts for about 40% of carbamazepine disposition, and this percentage is even greater in patients with induced epoxide pathway metabolism (Faigle and Feldmann 1995). The frequency distribution of carbamazepine's kinetic parameters is unimodal, consistent with CYP3A3/4 being the crucial isoform. With enzyme induction of the epoxide pathway (presumably via CYP3A3/4 induction), formation of carbamazepine-E triples, causing the carbamazepine-E/carbamazepine ratio to increase (Eichelbaum *et al.* 1985). Other metabolic pathways include aromatic hydroxylation (25%), which is apparently via CYP1A2, and glucuronide conjugation of the carbamoyl side chain (15%) (Staines *et al.* 2004) to yield inactive metabolites.

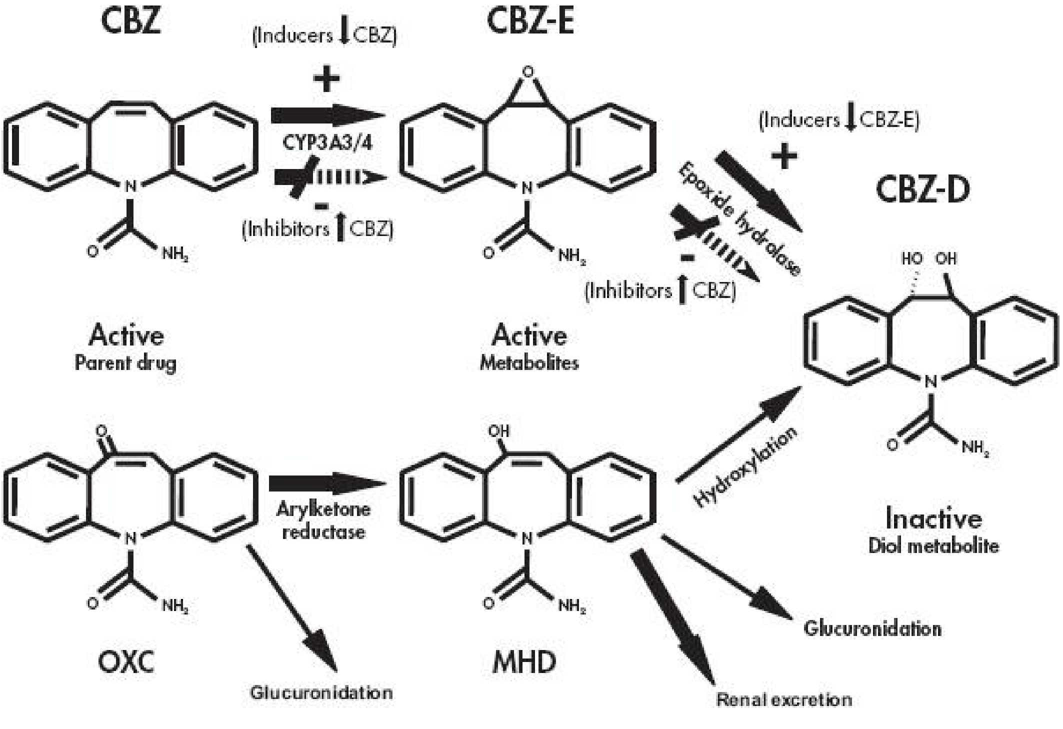
CBZ
(Inducers ↓CBZ)
+
CYP3A3/4
-
(Inhibitors ↑CBZ)
CBZ-E
(Inducers ↓CBZ-E)
+
Epoxide hydrolase
-
(Inhibitors ↑CBZ)
CBZ-D
HO OH
O
N
O
NH2
Active
Parent drug
Active
Metabolites
Inactive
Diol metabolite
OH
Arylketone reductase
Hydroxylation
OXC
MHD
Glucuronidation
Glucuronidation
Renal excretion

FIGURE 39-1. Carbamazepine (CBZ) and oxcarbazepine (OXC) metabolism.

+ = enzyme induction; [?] = enzyme inhibition; CBZ-D = carbamazepine-10,11-dihydro-dihydroxide; CBZ-E = carbamazepine-10,11-epoxide; CYP3A3/4 = cytochrome P450 3A3/4 isoenzyme; MHD = monohydroxy derivative.

Carbamazepine has erratic absorption and a bioavailability of approximately 80%. Tablets should not be stored above 30degC (86degF) and should be protected from light and moisture (Nightingale 1990; Novartis Pharmaceuticals 2015). Carbamazepine is about 75% bound to plasma proteins and has a moderate volume of distribution of approximately 1 L/kg. Before autoinduction of the epoxide pathway, the half-life of carbamazepine is about 24 hours and clearance is about 25 mL/minute.

After autoinduction (2-4 weeks into therapy), the half-life of carbamazepine decreases to approximately 8 hours and clearance increases to about 75 mL/minute. These changes may require dosage adjustment to maintain adequate blood concentrations and therapeutic effects. The active carbamazepine-E metabolite has a half-life of approximately 6 hours and is converted to an inactive diol (carbamazepineD) by epoxide hydrolase. The extended-release carbamazepine formulations given twice

daily yield steady-state carbamazepinetarget, with carbamazepine serum concentrations similar to those seen with the immediate-release formulation given four times daily (Garnett *et al.* 1998; Thakker *et al.* 1992), although clinical data support the use of once-nightly dosing for patients with mood disorders for help with sleep and daytime side effects.

When carbamazepine is used in the treatment of acute mania, two divergent clinical needs influence the rate of dosage titration. The need for rapid control of the manic syndrome should be balanced against the need to minimize adverse effects, which can be worsened with overly aggressive escalation of the carbamazepine dosage. Thus, although a loading-dose strategy may be tolerated and effective with valproate in the treatment of mania (Keck *et al.* 1993), the potential for neurotoxic adverse effects (e.g., CNS symptoms such as dizziness, somnolence, cognitive slowness, tremors, ataxia, and slurred speech) limits the use of such an aggressive approach with carbamazepine.

In inpatient treatment of mania, carbamazepine is commonly started at 400-800 mg/day in divided doses and increased as tolerated (by 200 mg/day every 1-4 days) to provide clinical efficacy. In controlled studies, the beaded extended-release capsule formulation was started at 200 mg bid and increased daily by 200 mg to a final dosage as high as 1,600 mg/day (Weisler *et al.* 2004, 2005). Managing dosage titration against adverse effects is more important than targeting a specific blood concentration range. The usual dosage range is 800-1,600 mg/day given in up to three or four divided doses with the immediate-release formulation. Extended-release formulations permit two divided doses per day and may even allow most or all of the daily dosage to be taken at bedtime for patients with mood disorder. Carbamazepine has a fairly rapid onset of antimanic efficacy. Thus, if clinical improvement has not occurred after 7-10 days, the clinician should consider augmentation or alternative strategies.

In a 6-month open-label extension of controlled studies in acute mania, carbamazepine beaded extended-release capsules were started at 200 mg bid and increased by 200 mg every 3 days (vs. every day in the acute studies) to a final dosage as high as 1,600 mg/day (Ketter *et al.* 2004). This approach decreased the incidence of CNS (dizziness, somnolence, ataxia), digestive system (nausea, vomiting), and dermatological (pruritus) adverse effects by approximately 50%.

In less acute situations such as depression or prophylaxis, carbamazepine is often started at 100-200 mg/night and is increased as necessary and tolerated by 200 mg every 4-7 days. Even more gradual initiation strategies may be necessary to alleviate adverse effects. Thus, starting with 50 mg (half of a chewable 100-mg tablet) at bedtime and increasing the daily dosage by 50 mg every few days can result in a better-tolerated initiation. Often, given dosages of carbamazepine may be better tolerated after 1 month of therapy, once autoinduction of carbamazepine metabolism has decreased the serum carbamazepine concentrations (Cereghino 1975) and accommodation and tolerance to adverse effects such as sedation have occurred. In two carbamazepine-versus-lithium maintenance studies, trough serum carbamazepine concentrations were maintained at 4-12 mg/mL, with a mean of 6.4 mg/mL (Greil *et al.* 1997) and 7.7 mg/mL (Denicoff *et al.* 1997).

Because carbamazepine dosages and serum and cerebrospinal fluid concentrations do not correlate with the drug's psychotropic efficacy (Post 1989; Post *et al.* 1983, 1984a), clinical management involves gradual upward titration until adequate therapeutic efficacy is achieved or adverse effects supervene. The 4-to 12-mg/mL serum carbamazepine concentration range used in epilepsy may be considered as a broad

target, with carbamazepine serum concentrations used as checks for pharmacokinetic problems, but frequent blood level monitoring is not required. The active carbamazepine-E metabolite can yield therapeutic and adverse effects similar to those of carbamazepine, but it is not detected in conventional carbamazepine assays.

In responders, a dose-response relationship may be evident, so slowly increasing carbamazepine dosages to maximize response in the absence of significant adverse effects would be an appropriate clinical strategy. However, if there is no hint of therapeutic response at moderate dosages, it is unlikely that increasing to very high dosages would be beneficial.

Oxcarbazepine

Oxcarbazepine is available in the United States as a proprietary product (Trileptal; Novartis Pharmaceuticals 2017) supplied in suspension (300 mg/5 mL) and tablet (150, 300, and 600 mg) formulations. FDA-approved generic products are available for both of these dosage forms. A novel once-daily extended-release formulation (Oxtellar XR; Supernus Pharmaceuticals 2018) has also been approved for the adjunctive treatment of partial seizures in adults and in children ages 6-17 years. Limited data suggest that this formulation has enhanced tolerability (Chung *et al.* 2016). Intramuscular and depot formulations of oxcarbazepine are not available.

Oxcarbazepine is 96% absorbed, and the modest effect of food on oxcarbazepine kinetics does not seem to be of therapeutic consequence (Degen *et al.* 1994). Oxcarbazepine is 60% bound to plasma proteins. Like carbamazepine, oxcarbazepine has a complex metabolism (Figure 39-1, bottom). Thus, oxcarbazepine is rapidly reduced to an active monohydroxy derivative (MHD) by cytosol arylketone reductase. The MHD form (also called licarbazepine) is 40% bound to plasma proteins, has a moderate volume of distribution of about 0.8 L/kg, and has a half-life of approximately 9 hours. Oxcarbazepine is eliminated primarily in the form of MHD (70%) and MHD glucuronide conjugates (20%), with a small proportion (10%) eliminated in the form of oxcarbazepine glucuronide conjugates and carbamazepineD.

Oxcarbazepine does not trigger autoinduction, and it causes substantially less heteroinduction than does carbamazepine. As described later in this chapter (see section "Drug-Drug Interactions"), medication interactions are thus less problematic with oxcarbazepine than with carbamazepine (Baruzzi *et al.* 1994).

Oxcarbazepine is started at 150 mg/day and increased every other day by 150 mg to a target of 1,200-1,600 mg/day in two to three divided doses. Further dosage increases up to 2,400 mg/day may be clinically indicated. In small trials of oxcarbazepine in acute mania, mean oxcarbazepine dosages were 1,400-2,400 mg/day (Emrich 1990; Emrich *et al.* 1983). As with carbamazepine, oxcarbazepine is titrated to the desired clinical effect as tolerated when used to treat patients with bipolar disorder, with the serum concentration range used in epilepsy considered a broad target and with oxcarbazepine serum concentrations used as checks for pharmacokinetic problems. Equipotent doses of oxcarbazepine range from 1.2 to 1.5 times the carbamazepine dose. For Oxtellar XR, all-HS (bedtime) dosing is not unreasonable.

Eslicarbazepine Acetate

Eslicarbazepine acetate is available in the United States as a proprietary product (Aptiom; Sunovion Pharmaceuticals 2013) supplied in tablet strengths of 200, 400, 600, and 800 mg. FDA-approved generic equivalent products are available. Extended-release, intramuscular, and depot formulations of eslicarbazepine acetate are not available.

Licarbazepine is the active MHD product of oxcarbazepine, and eslicarbazepine is the *S*-isomer of licarbazepine (Figure 39-2). Eslicarbazepine acetate is a prodrug of *S*-licarbazepine. Licarbazepine is 40% bound to plasma proteins, has a moderate volume of distribution (about 0.8 L/kg), and has a half-life of about 20-24 hours (Zaccara *et al.* 2015). Elimination is mainly through the kidneys, unchanged or glucuronidated (Zaccara *et al.* 2015). Eslicarbazepine acetate pharmacokinetics do not seem to be affected in patients with moderate hepatic impairment (Almeida *et al.* 2008).

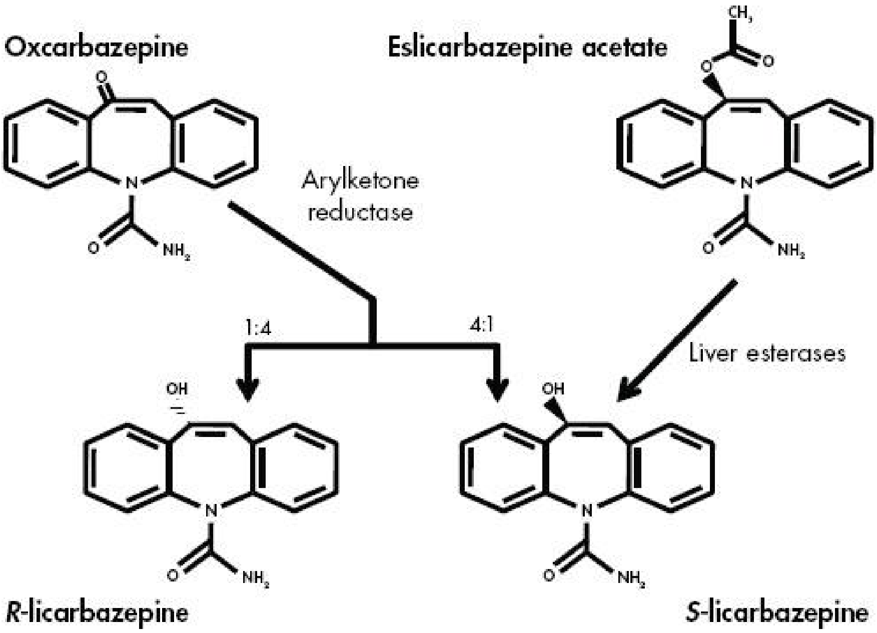

FIGURE 39-2. Oxcarbazepine and eslicarbazepine acetate metabolism.

Oxcarbazepine is metabolized to the active monohydroxy derivative as a racemic mixture with a higher (4:1) ratio of the *S*-enantiomer compared with the *R*-enantiomer. Eslicarbazepine acetate is rapidly metabolized to the common but specifically *S*-enantiomer of the monohydroxy derivative (Bialer 2006).

In a 2015 study evaluating the safety of two dosage-titration regimens of eslicarbazepine acetate in the treatment of patients with bipolar I disorder and acute mania, eslicarbazepine acetate was started at 600 or 800 mg/day and increased every 3 days by 600 or 800 mg to a target dosage of 1,800 or 2,400 mg/day, respectively. Despite the aggressive titration schedule, adverse effects were of mostly mild to moderate intensity but response did not exceed that of placebo (Grunze *et al.* 2015).

Transitioning a patient from oxcarbazepine to eslicarbazepine acetate would be expected to be relatively straightforward, with an oxcarbazepine/eslicarbazepine acetate dose ratio of 1:1, and could occur within 1 day. By contrast, transitioning a patient from carbamazepine to eslicarbazepine acetate would be considerably more complicated, with a carbamazepine/eslicarbazepine acetate dose ratio of 1:1.3, and would require at least 1-2 weeks, as clinically determined (Peltola *et al.* 2015).

Mechanisms of Action

Carbamazepine and oxcarbazepine have both structural and mechanistic similarities. However, these agents have such a diversity of biochemical effects that linking these mechanisms to their varying clinical actions presents a considerable challenge.

Carbamazepine

Although carbamazepine has a tricyclic structure like that of imipramine, the two agents have markedly different neurochemical, hepatic, and clinical effects. Carbamazepine lacks imipramine's major effects on monoamine reuptake and high affinity for histaminergic, cholinergic, adrenergic b, and dopamine receptors. However, carbamazepine has a wide range of other cellular and intracellular effects.

One useful way of considering carbamazepine's diverse mechanisms is from the perspective of onset of action (Post 1988). Carbamazepine's cellular actions with acute onset that might parallel the time course of clinical anticonvulsant effects include decreasing sodium influx and glutamate release, increasing potassium conductance, and interacting with peripheral benzodiazepine and a_2-adrenergic receptors. Acute or subchronic actions--such as increasing striatal cholinergic neurotransmission; decreasing adenylate cyclase activity stimulated by dopamine, norepinephrine, and serotonin; and decreasing turnover of dopamine, norepinephrine, and GABA--may be pertinent to carbamazepine's clinical antimanic effects. Finally, the actions requiring chronic administration--including increasing serum and urinary free cortisol, free tryptophan, substance P sensitivity, and adenosine A1 receptors and paradoxically decreasing cerebrospinal somatostatin--may be those that are most closely related to carbamazepine's clinical antidepressant effects.

Oxcarbazepine

Compared with the knowledge base on carbamazepine's mechanisms of action, less is known about oxcarbazepine (and thus eslicarbazepine acetate, given their common active molecules). Most evidence thus far suggests that oxcarbazepine's structural similarity to carbamazepine is paralleled by mechanistic similarity (Ambrosio *et al.*

2002). For example, oxcarbazepine, like carbamazepine, appears to decrease sodium (Benes *et al.* 1999; Wamil *et al.* 1994) and calcium (Stefani *et al.* 1995) influx, glutamate release (Ambrosio *et al.* 2001), and serum thyroxine concentrations (Isojarvi *et al.* 2001b); to increase potassium conductance (McLean *et al.* 1994) and dopaminergic (Joca *et al.* 2000) neurotransmission; and to block adenosine A_1 receptors (Deckert *et al.* 1993). However, there may be some mechanistic dissimilarities, particularly given the marked difference between oxcarbazepine and carbamazepine in the degree of hepatic enzyme induction. For example, oxcarbazepine seems to be a less potent modulator of voltage-gated calcium channels than is carbamazepine (Schmutz *et al.* 1994; Stefani *et al.* 1997). The general oxcarbazepine-carbamazepine mechanistic overlap is consistent with the hypothesis that these medications have generally similar

effects in bipolar disorder, which in turn is consistent with preliminary clinical observations; however, these similarities remain to be established in large controlled clinical studies.

Eslicarbazepine Acetate

Eslicarbazepine acetate and oxcarbazepine likely have a similar mode of action because they share the same main active metabolite licarbazepine--although the oxcarbazepine metabolite is racemic licarbazepine, whereas the eslicarbazepine acetate metabolite is exclusively the S-isomer of licarbazepine (Almeida and Soares-da-Silva 2007; Schutz *et al.* 1986). Thus, eslicarbazepine acetate behaves as a blocker of the voltage-gated sodium channel (Almeida and Soares-da-Silva 2007). Whereas eslicarbazepine acetate reduces voltage-gated sodium channel availability through enhancement of slow inactivation, carbamazepine acts by altering fast inactivation of the channel (Hebeisen *et al.* 2015). Eslicarbazepine and carbamazepine also differ with regard to submaximal GABA currents, Kv7.2 potassium channel outward currents, and high-and low-affinity Cav3.2 calcium channel inward currents (Keating 2014). Oxcarbazepine and eslicarbazepine acetate may have some mechanistic differences as well, with carbamazepine and oxcarbazepine enhancing excitatory synaptic transmission via antagonism of the adenosine A_1 receptor at therapeutic doses; eslicarbazepine acetate does so only at supratherapeutic high doses (Booker *et al.* 2015).

Indications and Efficacy

Seizure Disorders and Trigeminal Neuralgia

In the United States, carbamazepine (as immediate-release tablets, suspension, and Carbatrol extended-release capsules) is approved as monotherapy for the treatment of trigeminal neuralgia and complex partial, generalized tonic-clonic, and mixed seizure disorders (U.S. Food and Drug Administration 2023). Oxcarbazepine is approved for the treatment of partial seizures as monotherapy in adults and as adjunctive therapy in adults and children older than 4 years (U.S. Food and Drug Administration 2023). Eslicarbazepine is approved as monotherapy or adjunctive treatment for partial-onset seizures (U.S. Food and Drug Administration 2023).

Carbamazepine and oxcarbazepine seem to have overlapping anticonvulsant effects, with similar efficacy in patients with newly diagnosed epilepsy (Dam *et al.* 1989). However, there may be dissimilarities. For example, switching to oxcarbazepine may be effective for patients for whom carbamazepine results in an inadequate response or intolerable adverse effects (Beydoun *et al.* 2000; Van Parys and Meinardi 1994); adding oxcarbazepine may improve efficacy for patients whose symptoms respond inadequately to carbamazepine (Barcs *et al.* 2000; Glauser *et al.* 2000).

Acute Mania

The FDA approved a proprietary carbamazepine beaded extended-release capsule formulation (Equetro) for the treatment of acute manic and mixed episodes in patients with bipolar disorder in late 2004. Twenty-six controlled studies have investigated the efficacy of carbamazepine, oxcarbazepine, and eslicarbazepine acetate in acute mania (summarized in Table 39-1). In these studies, there is more compelling evidence for the efficacy of carbamazepine (18 studies encompassing 594 patients receiving carbamazepine) compared with that for oxcarbazepine (5 studies including 119 patients receiving oxcarbazepine) and ambiguous results with eslicarbazepine acetate (2 studies encompassing 146 patients receiving eslicarbazepine acetate).

TABLE 39-1. Carbamazepine (CBZ), oxcarbazepine (OXC), and eslicarbazepine acetate (ESL) in acute mania: 26 double-blind studies

Study	Design	CBZ/OXC/ESL (*N*)	Comparator (*N*)	Duration (days)	CBZ/OXC response	Comparator response

Study	Design	CBZ/OXC/ESL (*N*)	Comparator (*N*)	Duration (days)	CBZ/OXC response	Comparator response
Weisler *et al.* 2004	CBZ vs. PBO	101	103	21	42%	22%
Weisler *et al.* 2005	CBZ vs. PBO	122	117	21	61%	29%
Zhang *et al.* 2007	CBZ vs. PBO	41	21	84	88%	57%
Wagner *et al.* 2006	OXC vs. PBO	55	55	42	42%	26%
Ballenger and Post 1978; Post *et al.* 1987	PBO-CBZ-PBO	19	--	11-56	63%	Frequent relapse
Emrich *et al.* 1985	PBO-OXC-PBO	7	--	Varied	67%	--
Klein *et al.* 1984	CBZ vs. PBO adjunct (HAL)	14	13	35	71%	54%
Muller and Stoll 1984; Goncalves and Stoll 1985	CBZ vs. PBO adjunct (HAL)	6	6	21	CBZ > PBO	--
Gangadhar *et al.* 1987	CBZ vs. PBO adjunct (Li)	5	5	28	CBZ > PBO	--
Moller *et al.* 1989	CBZ vs. PBO adjunct (HAL)	11	9	21	CBZ = PBO	--
Okuma *et al.* 1989	CBZ vs. PBO adjunct	82	80	28	48%	30%

Study	Design	CBZ/OXC/ESL (*N*)	Comparator (*N*)	Duration (days)	CBZ/OXC response	Comparator response
	(FGA)					
Okuma *et al.* 1979	CBZ vs. FGA (CPZ)	32	28	21-35	66%	54%
Grossi *et al.* 1984	CBZ vs. FGA (CPZ)	18	19	21	67%	76%
Emrich 1990	OXC vs. FGA (HAL)	19	19	14	OXC = HAL	--
Stoll *et al.* 1986	CBZ vs. FGA (HAL) adjunct (CPZ)	14	18	21	86%	67%
Brown *et al.* 1989	CBZ vs. FGA (HAL) adjunct (CPZ)	8	9	28	75%	33%
Muller and Stoll 1984	OXC vs. FGA (HAL) adjunct (HAL)	10	10	14	OXC = HAL	--
Lerer *et al.* 1987	CBZ vs. Li	14	14	28	29%	79%
Small *et al.* 1991	CBZ vs. Li	24	24	56	33%	33%
Emrich 1990	OXC vs. Li	28	24	14	OXC = Li	--
Kakkar *et al.* 2009	OXC vs. DVPX	30	30	84	OXC = DVPX	--
Lenzi *et al.* 1986	CBZ vs. Li adjunct (CPZ)	11	11	19	73%	73%
Lusznat *et al.* 1988	CBZ vs. Li adjunct	22	22	42	CBZ = Li	--

Study	Design	CBZ/OXC/ESL (*N*)	Comparator (*N*)	Duration (days)	CBZ/OXC response	Comparator response
	(CPZ, HAL)					
Okuma *et al.* 1990	CBZ vs. Li adjunct (FGA)	50	51	28	62%	59%
Grunze *et al.* 2015	ESL vs. PBO	120	40	21	63%	50%
Grunze *et al.* 2015	ESL vs. PBO	26	11	21	77%	91%
Total		**889**	**739**			
Response rates[a]	CBZ/OXC/ESL monotherapy				**58%** (333/579)	
	FGA monotherapy					**64%** (30/47)
	Li monotherapy					**50%** (19/38)
	PBO monotherapy					**33%** (113/347)
Response rates[a]	CBZ/OXC adjunctive				**59%** (106/179)	
	FGA adjunctive					**56%** (15/27)
	Li adjunctive					**61%** (38/62)
	PBO adjunctive					**33%** (31/93)

Note. -- = not known; CPZ = chlorpromazine; DVPX = divalproex; FGA = first-generation antipsychotic; HAL = haloperidol; Li = lithium; PBO = placebo.

[a] Weighted means of patients with response data.

Carbamazepine and Oxcarbazepine

Two trials reporting that a proprietary carbamazepine beaded extended-release capsule formulation (Equetro) was superior to placebo are of particular interest, because they used a randomized double-blind, placebo-controlled design (Weisler *et al.* 2004, 2005) and led to the FDA indication for the treatment of acute manic and mixed episodes in patients with bipolar disorder. These reports are consistent with multiple earlier studies using placebo-drug-placebo, active comparator (lithium or first-generation antipsychotics), and adjunctive designs.

Thus, across studies using diverse paradigms (see Table 39-1), overall antimanic response rates with carbamazepine were generally comparable to those seen with lithium or first-generation antipsychotics or in other studies with valproate (Ketter 2010). Taken together, this collection of clinical trials provides substantial evidence for the acute antimanic efficacy of carbamazepine and some preliminary evidence for the acute antimanic efficacy of oxcarbazepine. Interestingly, the body of existing data for carbamazepine seems to be greater than that initially used by the FDA to approve lithium for the treatment of acute mania.

For carbamazepine, improvement appears to occur across the entire manic syndrome and does not seem to be attributable to nonspecific sedative properties because patients often show dramatic clinical improvement in the absence of marked sedation. Carbamazepine and oxcarbazepine are frequently used in combination with other medications in the acute treatment of mania, so knowledge of carbamazepine's extensive and oxcarbazepine's more limited drug-drug interactions (as described in the section "Drug-Drug Interactions") is often required to achieve optimal outcomes.

Eslicarbazepine Acetate

In two 3-week studies of eslicarbazepine acetate in acute mania, the drug did not separate from placebo on the primary outcome measure of Young Mania Rating Scale score change; however, Clinical Global Impression Scale score changes were suggestive of efficacy in one study (Grunze *et al.* 2015). High rates of placebo response and poor study recruitment (leading to premature study termination) may have contributed to treatment failure in the second study (Grunze *et al.* 2015).

Acute Depression

Limited controlled data exist regarding the acute antidepressant effects of carbamazepine (Table 39-2). To date, there are no published controlled studies examining the antidepressant effects of oxcarbazepine or eslicarbazepine acetate. However, in a study in which 10 patients with depression initially responded when carbamazepine was substituted for placebo, response was reconfirmed by relapse occurring when placebo was again given, and a subsequent re-response to blind retreatment with carbamazepine was observed (Ballenger and Post 1978). Although carbamazepine seems to have weaker antidepressant than antimanic properties, some evidence suggests that it may provide antidepressant benefit for about one-third of individuals with treatment-resistant depression (Neumann *et al.* 1984; Post *et al.* 1986; Small 1990). In a Chinese study, carbamazepine produced a response rate closer to two-thirds in patients with non-treatment-resistant depression (Zhang *et al.* 2007). Unfortunately, most of these studies are limited by their use of small samples of heterogeneous patients with highly treatment-resistant depression (both bipolar and unipolar).

TABLE 39-2. Carbamazepine (CBZ) in acute depression: four controlled studies

Study	**Design**	**CBZ (*N*)**	**Comparator (*N*)**	**Duration (days)**	**CBZ response**	**Comparator response**
Post *et al.* 1986	PBO-CBZ-PBO (24 BP, 11 UP)	35	35	Median 45	34%	--
Zhang *et al.* 2007	CBZ vs. PBO	47	23	84	64%	35%
Small 1990	CBZ/CBZ + Li vs. Li (4 BP, 24 UP)	NS	NS	28	32%	13%
Neumann *et al.* 1984	CBZ vs. TMI (5 BP, 5 UP)	5	5	28	CBZ = TMI	--

Note. -- = not known; BP = bipolar; Li = lithium; NS = not stated; PBO = placebo; TMI = trimipramine; UP = unipolar.

Maintenance and Relapse-Prevention Treatment

Carbamazepine and Oxcarbazepine

A series of 18 double-blind randomized, open randomized, or otherwise partially controlled studies examined the efficacy of carbamazepine and oxcarbazepine in maintenance treatment of bipolar disorder (summarized in Table 39-3). The 15 carbamazepine trials are consistent with a very substantial open literature suggesting that this drug is effective in preventing mood episodes when administered during long-term treatment either alone or in combination with lithium in previous lithium nonresponders (see Table 39-3). Indeed, five reviews of different subsets of studies included in Table 39-3 broadly indicated that carbamazepine and lithium monotherapy had comparable prophylactic effects in patients with bipolar disorder (Ceron-Litvoc *et al.* 2009; Dardennes *et al.* 1995; Davis *et al.* 1999; Hirschfeld and Kasper 2004; Smith *et al.* 2007). One study comparing carbamazepine with oxcarbazepine randomly assigned 153 patients with symptoms that responded inadequately to lithium, and the investigators reported that oxcarbazepine was superior to carbamazepine on all measures at weeks 4 and 8 (Juruena *et al.* 2009).

TABLE 39-3. Carbamazepine (CBZ) and oxcarbazepine (OXC) in maintenance treatment of bipolar disorder: 18 controlled or quasi-controlled studies

Study	Design	CBZ/OXC (*N*)	Comparator (*N*)	Duration (years)	CBZ/OXC response	Comparator response
Okuma *et al.* 1981	CBZ vs. PBO (B, R)	12	10	1	60%	22%
Ballenger and Post 1978; Post *et al.* 1983	CBZ vs. PBO (B, M)	7	7	1.7	86%	NS
Placidi *et al.* 1986	CBZ vs. Li (B, R)	20	16	[?] 3	67%	67%
Watkins *et al.* 1987	CBZ vs. Li (B, R)	19	18	1.5	84%	83%
Lusznat *et al.* 1988	CBZ vs. Li (B, R)	16	15	[?] 1	56%	29%
Coxhead *et al.* 1992	CBZ vs. Li (B, R)	13	15	1	54%	47%
Bellaire *et al.* 1988	CBZ vs. Li (R)	46	52	1	CBZ = Li	NS
Greil *et al.* 1997	CBZ vs. Li (R)	70	74	2.5	45%	65%
Berky and Kovacs 1998	CBZ vs. Li (R)	84	84	1	CBZ = Li	NS

Note. B = blinded; C = crossover; Li = lithium; M = mirror image; NR = not randomized; NS = not stated; PBO = placebo; R = randomized; R? = possibly randomized.

[a] Weighted means of patients with response data.

Study	Design	CBZ/OXC (*N*)	Comparator (*N*)	Duration (years)	CBZ/OXC response	Comparator response
Hartong *et al.* 2003	CBZ vs. Li (R)	50	44	2	58%	73%
Di Costanzo and Schifano 1991	CBZ + Li vs. Li (R)	8	8	[?] 5	CBZ + Li > Li	NS
Mosolov 1991	CBZ vs. Li (R?)	30	30	[?] 1	73%	70%
Cabrera *et al.* 1986	OXC vs. Li (R)	4	6	[?] 22	75%	100%
Elphick *et al.* 1988	CBZ vs. Li (B, C)	8	11	0.75	38%	73%
Denicoff *et al.* 1997	CBZ vs. Li (B, C)	46	50	1	33%	55%
Kishimoto and Okuma 1985	CBZ vs. Li (C)	18	18	[?] 2	CBZ > Li	NS
Wildgrube 1990	OXC vs. Li (NR)	8	7	[?] 33	33%	67%
Vieta *et al.* 2008	OXC vs. PBO adjunct (B, R)	26	29	1	50%	34%
Total		**485**	**486**			
Response rates[a]	CBZ/OXC				**54%** (178/329)	
	Li					**64%** (185/286)
	PBO					**32%** (12/38)

Note. B = blinded; C = crossover; Li = lithium; M = mirror image; NR = not randomized; NS = not stated; PBO = placebo; R = randomized; R? = possibly randomized.

[a] Weighted means of patients with response data.

Carbamazepine may have equal *prophylactic* antidepressant and antimanic efficacy compared with its less potent *acute* antidepressant vs antimanic effects. In contrast, data regarding the efficacy of oxcarbazepine in preventing new mood episodes in patients with bipolar disorder are more limited (Cabrera *et al.* 1986; Vieta *et al.* 2008; Wildgrube 1990). A 2008 Cochrane Review assessed the available data as inadequate to recommend oxcarbazepine in the maintenance treatment of bipolar disorder (Vasudev *et al.* 2008).

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In one study, the overall analysis suggested that maintenance treatment was more effective with lithium than with carbamazepine (Greil *et al.* 1997). However, subgroup differences may exist. For example, lithium may be more effective for patients with "classical" bipolar disorder (e.g., bipolar I disorder with no mood-incongruent delusions, psychotic features, or comorbidity), whereas carbamazepine may be more effective for patients with "nonclassical" bipolar disorder (e.g., bipolar II disorder, DSM-IV [American Psychiatric Association 1994] bipolar disorder not otherwise specified, bipolar disorder with mood-incongruent delusions, and anxiety or substance abuse comorbidity) (Greil *et al.* 1998).

In another study, lithium maintenance treatment appeared to be more effective than carbamazepine for patients with no more than 6 months of prior exposure to either agent (Hartong *et al.* 2003). However, this advantage was offset by more early discontinuations in the lithium group, so that similar proportions (about one-third) of patients in both groups completed 2 years with no episode. Patients taking lithium versus carbamazepine tended to have a somewhat greater risk of episodes in the first 3 months and markedly less risk of episodes after the first 3 months, with a recurrence risk of only 10% per year with lithium after the first 3 months. Patients taking carbamazepine had a more consistent rate of relapse or recurrence of approximately 40% per year.

Some carbamazepine relapse-prevention trials have been criticized for their methodological limitations (Murphy *et al.* 1989), although such difficulties are common in maintenance studies. (For example, divalproex and lithium failed to separate from placebo on the primary efficacy measure in a 1-year maintenance study [Bowden *et al.* 2000], a result at least partially attributable to methodological problems.) Taken together, this collection of randomized placebo-controlled, placebo-drug-placebo, and lithium comparator studies and trials in rapid-cycling and lithium-resistant populations provides substantial evidence for the preventive efficacy of carbamazepine (Prien and Gelenberg 1989). Carbamazepine may be effective for some individuals with valproate-resistant illness (Post *et al.* 1984b), and the carbamazepine-valproate combination may be effective for patients who experience little or no response to either agent alone (Keck *et al.* 1992; Ketter *et al.* 1992).

In a retrospective study, 22 of 34 patients (65%) had treatment-resistant bipolar disorder that responded to primarily adjunctive open carbamazepine acutely. However, only 9 of the 22 (41%) were considered probable or clear responders when assessed 3-4 years later (Frankenburg *et al.* 1988). Post and colleagues suggested that the loss of carbamazepine prophylactic efficacy over time may be related to a unique form of contingent tolerance (Post and Weiss 2011; Post *et al.* 1990). In these instances, techniques such as switching to another treatment regimen with a different mechanism of action or returning later to carbamazepine (after a period of not taking it) are worth considering based on case reports and anecdotal observations.

Eslicarbazepine Acetate

A 6-month continuation study investigated the efficacy of three different dosages of eslicarbazepine acetate (300, 900, and 1,800 mg/day) in preventing symptom recurrence in patients with bipolar disorder who had participated in the earlier placebo-controlled studies of eslicarbazepine acetate in acute mania. Of the 85 patients who experienced a symptom response during acute treatment and were randomly assigned to one of three dosage groups, at least 50% did not show any clinical worsening; however, there was no significant difference between dosage groups (Grunze *et al.* 2015).

Response Predictors

Predictors of carbamazepine response have only been preliminarily elucidated. Carbamazepine can be effective for patients with a history of lithium unresponsiveness or intolerance (Okuma *et al.* 1979; Post *et al.* 1987). Nonclassical bipolar disorder (Greil *et al.* 1998; Small *et al.* 1991) and stable or decreasing episode frequency (Post *et al.* 1990) may be associated with carbamazepine response. Patients with a history of affective illness in first-degree relatives may experience a preferential response to lithium, whereas the converse may be the case for carbamazepine (Ballenger and Post 1978; Post *et al.* 1987). Patients with comorbid neurological or substance abuse problems and illness that responds inadequately to lithium may experience a response to carbamazepine or valproate (Himmelhoch 1987; Himmelhoch and Garfinkel 1986). Preliminary observations indicate that baseline cerebral (left insula) hypermetabolism may be a marker of carbamazepine antidepressant response, in contrast with left insula hypometabolism for nimodipine response (Ketter *et al.* 1999). Reports vary with respect to the relationship between carbamazepine response and dysphoric manic presentations (Lusznat *et al.* 1988; Post *et al.* 1989) or illness severity (Post *et al.*

1987; Small *et al.* 1991). Antidepressant responses to carbamazepine may be seen in patients with more severe depression, more discrete depressive episodes, less chronicity, and greater decreases in serum thyroxine concentrations with carbamazepine (Post *et al.* 1986, 1991).

Although the initial studies of Post *et al.* and Okuma *et al.* indicated that rapid-cycling illness was responsive to carbamazepine for some patients (Okuma 1983; Okuma *et al.* 1981; Post *et al.* 1987), other investigators found less robust results (Dilsaver *et al.* 1993; Joyce 1988). As with lithium, later studies by Okuma *et al.* reported a lower carbamazepine maintenance response rate in rapid-cycling compared with non-rapid-cycling illness (Okuma 1993). However, even these patients with rapid cycling had a higher carbamazepine response rate (40%) than those reported with other agents in other studies. Denicoff *et al.* (1997) also observed that patients with a history of rapid cycling had a lower response rate to maintenance carbamazepine compared with those without such a history (19% vs. 54%), but rapid cyclers did well with the combination of lithium and carbamazepine.

Side Effects and Toxicology

Baseline evaluation of patients with bipolar disorder includes not only psychosocial assessment but also a general medical evaluation. Assessment commonly includes the following: history, physical examination, complete blood count with differential and platelets, electrolytes, toxicology, and tests for pregnancy and renal, hepatic, and thyroid function as well as other chemistries and electrocardiograms as clinically indicated (American Psychiatric Association 2002). Such evaluation provides baseline values for parameters that influence decisions about the choice of medication and intensity of clinical and laboratory monitoring.

Carbamazepine

Adverse effects can impact the utility of carbamazepine in the treatment of bipolar disorder, but most can be managed with careful individualized dose titration. In a pooled analysis of two multicenter acute mania FDA registration studies of a proprietary extended-release capsule formulation of carbamazepine (Equetro), the number needed to harm for somnolence was 6 and the number for at least 7% weight gain was 23 (Ketter *et al.* 2011). This result suggests that neurocognitive adverse effects might limit carbamazepine utility more than weight gain (Ketter 2015). However, the sedative side effects were assessed when patients were dosed twice a day, and all-nighttime or mostly-nighttime dosing should markedly lessen this problem. Some patients may tolerate carbamazepine better than other agents, particularly during longer-term treatment, because it seems to have a low propensity to cause adverse effects, such as weight gain and metabolic disturbance, that can limit the utility of some other agents (Akiskal *et al.* 2005; Ketter 2015).

Carbamazepine has several common dose-related adverse effects that generally can be minimized by attention to drug-drug interactions and gradual dose titration or reversed by decreasing dosage. At high doses, patients can develop neurotoxicity with sedation, ataxia, diplopia, and nystagmus, particularly early in therapy with acute-release formulations, before the autoinduction process is complete and tolerance to the CNS adverse effects of carbamazepine develops. Because there is wide interindividual variation in susceptibility to adverse effects at any given concentration, it is most useful clinically to titrate doses against each patient's adverse effects rather than targeting a fixed dosage or serum concentration range.

Neurotoxic effects that emerge 1-2 hours after an individual dose often signal that the adverse-effect threshold has been exceeded and that dose redistribution (i.e., spreading out the doses or giving more of the dose at bedtime) or dosage reduction may be required. Use of extended-release formulations may attenuate carbamazepine peak serum concentrations, enhancing tolerability.

Carbamazepine commonly causes benign hematological (leukopenia, thrombocytopenia), dermatological (rash), electrolyte (asymptomatic hyponatremia), and hepatic (transaminase elevations) problems. Analogous serious problems are much less common. For example, mild leukopenia and benign rash occur for up to 1 in 10 patients, with only a slight possibility that these usually benign phenomena are heralding malignant aplastic anemia and Stevens-Johnson syndrome, which is seen in about 1 in 100,000 patients (Kramlinger *et al.* 1994; Tohen *et al.* 1995). Bone loss from taking anticonvulsants, including carbamazepine, was significantly prevented for patients receiving risedronate versus placebo as add-ons to calcium and vitamin D (Lazzari *et al.* 2013).

In view of the risk of rare but serious decreases in blood counts, which warrant a black box warning in the carbamazepine prescribing information, it is important to alert patients to seek immediate medical evaluation if they develop signs and symptoms of possible hematological reactions such as fever, sore throat, oral ulcers, petechiae, and easy bruising or bleeding. Hematological monitoring must be intensified for patients with low or marginal leukocyte counts, and carbamazepine is generally discontinued if the leukocyte count falls below 3,000/mL or the granulocyte count is less than 1,000/mL. In the instance of benign leukopenia, the addition of lithium can

increase the neutrophil count back toward normal (Kramlinger and Post 1990), but this strategy is not likely to be helpful for the suppression of red cells or platelets, which likely indicates a more problematic process.

Serious rash may occur in about 1 in 10,000-100,000 patients. The risk of serious and sometimes fatal dermatological reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, may be increased 10-fold in certain Asian populations and has been strongly linked to the human leukocyte antigen *HLA-B*1502* allele (Novartis Pharmaceuticals 2015). Thus, the U.S. prescribing information includes a black box warning that individuals of Asian ancestry should be genetically tested for *HLA-B*1502* and that carriers of this allele should not be treated with carbamazepine. In addition, a 12-fold increased risk of drug-induced hypersensitivity syndrome (also called drug rash with eosinophilia and systemic symptoms) has been linked to *HLA-A*3101* in white individuals of northern European descent (McCormack *et al.* 2011).

Given the risk of serious rash, patients should be alerted to seek medical attention immediately if a rash develops. In particular, rash in patients presenting with systemic illness or involvement of the eyes, mouth, or bladder (dysuria) constitutes a medical emergency: carbamazepine should be discontinued immediately, and the patient should be assessed emergently (Scaparrotta *et al.* 2011). For more benign presentations, carbamazepine is generally discontinued because there is little ability to predict which cases will progress to more severe, potentially life-threatening problems. However, in rare instances of resistance to other medications except carbamazepine, a repeat trial of carbamazepine with a course of prednisone has usually been well tolerated (Murphy *et al.* 1991; Vick 1983). A substantial number of patients with carbamazepine-induced rash may not develop a rash on re-exposure (even without prednisone coverage) but if a rash develops again, it usually appears more rapidly than the first occurrence. Only 25%-30% of patients who develop a rash with carbamazepine also develop a rash (cross-sensitivity) with oxcarbazepine.

Carbamazepine, in common with multiple other anticonvulsant medications (including oxcarbazepine and eslicarbazepine acetate), may increase the risk of suicidality, including suicidal behavior or ideation. Data from controlled trials of anticonvulsant medications compared with placebo showed a 1.5-fold increased risk from 0.57% to 0.85% for psychiatric patients (Novartis Pharmaceuticals 2015).

Because of the risk of rare hepatitis, patients should be advised to seek medical evaluation immediately if they develop malaise, abdominal pain, or other marked gastrointestinal symptoms. In general, carbamazepine (like other anticonvulsants) should be discontinued if liver function values exceed three times the upper limit of the normal range (Martinez *et al.* 1993).

Carbamazepine may affect cardiac conduction and should be used with caution in patients with cardiac disorders such as heart block. A baseline electrocardiogram is worth considering if the patient has a history of cardiac abnormalities or arrhythmias.

Conservative laboratory monitoring during carbamazepine therapy includes baseline studies and evaluation of complete blood count, differential, platelets, and hepatic indices at treatment initiation, then biweekly (at 2, 4, 6, and 8 weeks), and then every 3 months (American Psychiatric Association 1994, 2002); however, much less frequent monitoring is typically practiced in neurology and followed by psychiatrists. Most of the serious hematological reactions occur within the first 3 months of therapy (Tohen *et al.* 1995). In contemporary clinical practice, clinically indicated

monitoring (e.g., when a patient becomes ill with a fever) is emphasized over scheduled monitoring. Patients who have abnormal or marginal indices at any point merit careful scheduled and clinically indicated monitoring. The U.S. prescribing information for the carbamazepine beaded extended-release capsule formulation recommends the following: obtaining a baseline complete blood count including platelets, possibly reticulocytes, possibly serum iron, and hepatic function tests; closely monitoring patients with low or decreased white blood cell counts or platelets; and considering discontinuation of carbamazepine if evidence indicates bone marrow depression (Validus Pharmaceuticals 2021). Serum carbamazepine concentrations are typically assessed at steady state and then as indicated by inefficacy or adverse effects, although frequent blood level monitoring to inform efficacy is not needed. An important clinical note is that because of autoinduction, carbamazepine concentrations may decrease during the first 2-3 weeks after treatment initiation (Eichelbaum *et al.* 1975), thus potentially requiring readjustment of steady-state dosing.

Dividing or reducing dosages, rescheduling individual doses in relation to mealtimes, and changing formulations can attenuate carbamazepine-induced gastrointestinal disturbance. The carbamazepine oral suspension may have more proximal absorption and thus may exacerbate upper gastrointestinal adverse effects (nausea and vomiting) or attenuate lower gastrointestinal effects (diarrhea). The reverse holds for extended-release preparations.

Weight gain and obesity are important clinical concerns in the management of bipolar disorder. Medications and the hyperphagia, hypersomnia, and anergy commonly seen in bipolar depression can contribute to this important obstacle to optimal outcomes. Carbamazepine is less likely than lithium (Coxhead *et al.* 1992; Denicoff *et al.* 1997) or valproate (Mattson *et al.* 1992) to cause weight gain. In one study, carbamazepine caused weight gain in patients with depression (but not mania), which seemed to be related to the degree of depression relief (Joffe *et al.* 1986). Nevertheless, in view of its relatively benign effect on weight, carbamazepine may provide an important alternative to other mood stabilizers for patients who struggle with weight gain and obesity. It is also important to emphasize that response to anticonvulsants is not a class effect in mania, and some patients with mania that does not respond to valproate may obtain a response with carbamazepine (Post *et al.* 1984b, 2007).

Carbamazepine can induce hyponatremia, which may be well tolerated by some younger patients but can be problematic at high doses and for elderly individuals. If an elderly patient develops confusion, serum sodium should be assessed. In rare instances, water intoxication and seizures can occur. In some cases, hyponatremia can be effectively counteracted or prevented with the addition of lithium or the antibiotic demeclocycline (Ringel and Brick 1986).

Carbamazepine increases plasma high-density lipoprotein (O'Neill *et al.* 1982) and total cholesterol (Brown *et al.* 1992) concentrations. However, the high-density lipoprotein/total cholesterol ratio does not change (O'Neill *et al.* 1982). Thus, carbamazepine-induced increases in total cholesterol are not likely to be clinically problematic in relation to atherosclerosis (Brown *et al.* 1992).

Carbamazepine seems to reduce serum concentrations of both female and male sex hormones (Verrotti *et al.* 2011), and higher-dosage formulations of birth control pills are likely to be needed. In common with several other anticonvulsants, carbamazepine may adversely affect bone density (Verrotti *et al.* 2010).

Previous studies show that carbamazepine is teratogenic (former FDA Pregnancy Category D) and is associated with low birth weight, craniofacial deformities, digital hypoplasia, and spina bifida (in approximately 3% of births; Jones *et al.* 1989; Rosa 1991). Folate supplementation may attenuate the risk of spina bifida, and fetal ultrasound studies may allow early detection. In one study of children born to women with epilepsy, in utero exposure to carbamazepine or valproate, but not to lamotrigine, had a detrimental effect on child neurodevelopment, although carbamazepine seemed less likely than valproate to cause major developmental delays (Cummings *et al.* 2011).

Carbamazepine is present in breast milk at concentrations about half those in maternal blood but may not accumulate in fetal blood (Froescher *et al.* 1984; Kuhnz *et al.* 1983; Pynnonen *et al.* 1977; Shimoyama *et al.* 2000). Clinicians may prefer to avoid the minor risks of exposing infants to carbamazepine in breast milk (Frey *et al.* 2002), and some may discourage breastfeeding among women taking carbamazepine (Novartis Pharmaceuticals 2015).

Oxcarbazepine

As with carbamazepine, adverse effects may limit oxcarbazepine therapy. However, oxcarbazepine may have tolerability advantages compared with carbamazepine (Dam *et al.* 1989), perhaps related in part to the absence of the carbamazepine-E metabolite. Of note, oxcarbazepine lacks black box warnings regarding serious rash, blood dyscrasias, or tissue typing, although it still has the class warning regarding increased risk of suicidality. Compared with carbamazepine, oxcarbazepine seems to have a lower propensity to cause neurotoxicity and rash. Approximately 75% of patients who develop a rash with carbamazepine will tolerate oxcarbazepine. Oxcarbazepine does not appear to require hematological monitoring.

Oxcarbazepine, like carbamazepine, may cause transaminase elevations and gastrointestinal adverse effects, but there is less weight gain than with valproate (Rattya *et al.* 1999) and less impact on lipids than with carbamazepine (Isojarvi *et al.* 1994). Hyponatremia is the one side effect that occurs more commonly with oxcarbazepine (Friis *et al.* 1993) than with carbamazepine (Isojarvi *et al.* 2001a). Although hyponatremia is often asymptomatic (Reinstein *et al.* 2002), clinicians should provide regular monitoring of serum sodium levels for elderly patients taking high dosages of oxcarbazepine.

Compared with carbamazepine, oxcarbazepine has less impact on female hormone blood concentrations, likely because of its less marked hepatic enzyme induction. However, oxcarbazepine induction of female hormone metabolism may still decrease the efficacy of hormonal contraceptives, which should be countered with dose increases (Fattore *et al.* 1999; Kramer *et al.* 1992). Oxcarbazepine, in common with carbamazepine and several other anticonvulsants, may adversely affect bone density (Verrotti *et al.* 2010).

To date, oxcarbazepine, in contrast with carbamazepine, has not been associated with congenital malformations in humans (former FDA Pregnancy Category C). Whether this is because of fewer oxcarbazepine exposures or the absence of the carbamazepine-E metabolite (rendering oxcarbazepine less teratogenic) is unknown. Oxcarbazepine is present in breast milk; therefore, as with carbamazepine, clinicians may prefer to avoid the risk of exposing infants to oxcarbazepine in breast milk and

may wish to discourage breastfeeding in women taking oxcarbazepine (Novartis Pharmaceuticals 2017)).

Eslicarbazepine Acetate

Adverse effects may limit oxcarbazepine therapy as with carbamazepine, but structural advantages may result in better tolerability with eslicarbazepine acetate (Almeida and Soares-da-Silva 2007). The most commonly reported adverse effects from two epilepsy registration studies included somnolence, dizziness, vertigo, ataxia, abnormal coordination, diplopia, fatigue, and headache (Sunovion Pharmaceuticals 2013). The risk of rash was low (about 1%). The risk of hyponatremia with eslicarbazepine acetate is unknown, with rates ranging from 0.6% to 1.3% in premarketing trials (Zaccara *et al.* 2015) and rates as high as 3% in postmarketing studies (Massot *et al.*

2014). Significant decreases in sodium levels ([?] 10 mEq/L) were more common with eslicarbazepine acetate than with placebo (Sunovion Pharmaceuticals 2013). Eslicarbazepine acetate may increase the QT interval on electrocardiograms (Vaz-Da-Silva *et al.* 2012).

Importantly, eslicarbazepine acetate, similar to oxcarbazepine, lacks black box warnings for serious rash, blood dyscrasias, or tissue typing. However, eslicarbazepine acetate still has the (non-black box) class warning regarding increased risk of suicidality.

To date, eslicarbazepine acetate, like oxcarbazepine, has not been associated with congenital malformations in humans (former FDA Pregnancy Category C). Eslicarbazepine acetate is excreted in breast milk (Sunovion Pharmaceuticals 2013).

Drug-Drug Interactions

Combination therapy is common in bipolar disorder, with up to two-thirds of patients taking more than one medication concurrently (Kupfer *et al.* 2002). Patients with treatment-resistant illness may require a stepped-care approach (Figure 39-3), and they seem to be receiving increasingly complex medication regimens (Frye *et al.* 2000). Carbamazepine, and to a lesser extent oxcarbazepine, has clinically significant drug-drug interactions that increase the complexity of managing bipolar disorder.

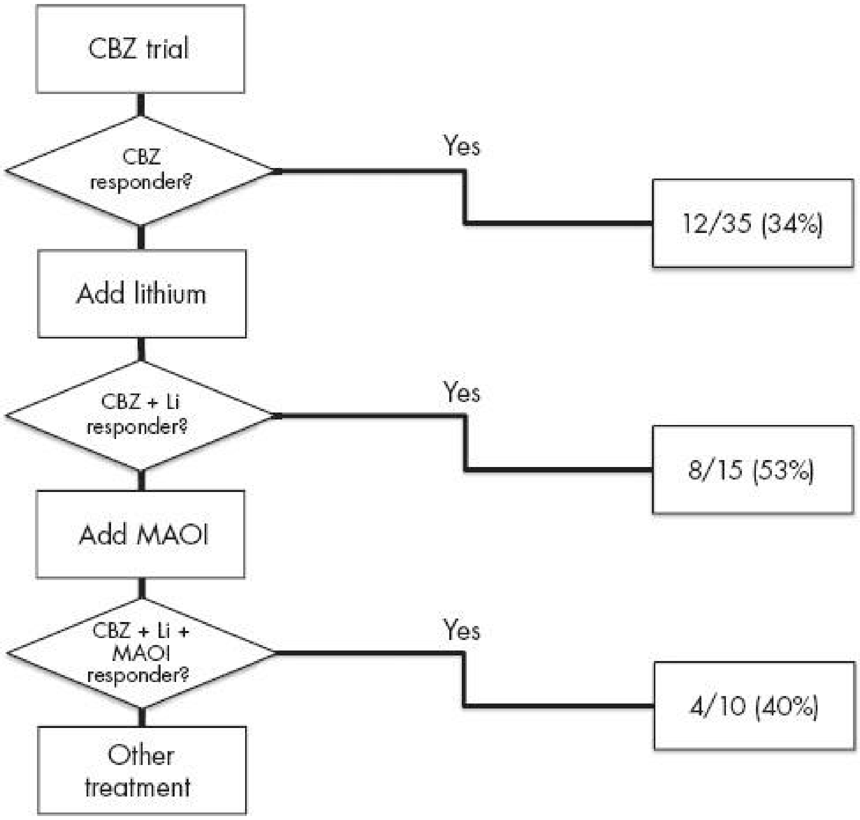

FIGURE 39-3. Stepped-care approach to bipolar depression.

Composite schema of results from three different studies in which patients with bipolar depression received carbamazepine (CBZ) monotherapy (Post *et al.* 1986), lithium (Li) added to carbamazepine (Kramlinger and Post 1989b), or a monoamine oxidase inhibitor (MAOI) added to carbamazepine with or without lithium (Ketter *et al.* 1995b). Each successive intervention resulted in additional efficacy.

Carbamazepine

The pharmacokinetic properties of carbamazepine are typical of older enzyme-inducing anticonvulsants but are atypical among medications prescribed by psychiatrists. Carbamazepine necessitates special care when used to treat patients who are concurrently taking other medications (Ketter *et al.* 1991a, 1991b). Three major principles appear to make important contributions to carbamazepine drug-drug interactions:

1. **Carbamazepine is a robust inducer of catabolic enzymes (including CYP3A3/4) and decreases the serum concentrations of many medications, including carbamazepine itself** (Table 39-4). Carbamazepine induces not only CYP3A3/4 and conjugates but also presumably other uncharacterized CYP isoforms. Thus, carbamazepine decreases serum concentrations of carbamazepine

itself (autoinduction) (Eichelbaum *et al.* 1975) and of other medications (heteroinduction); for example, it may cause major reductions in serum levels of methylphenidate (Behar *et al.* 1998). If carbamazepine is taken concurrently with certain medications, carbamazepine-induced decreases in serum concentrations can render these medications less effective (Table 39-4). Moreover, if carbamazepine is discontinued, serum concentrations of these other medications can increase, potentially leading to adverse effects.

2. **Carbamazepine metabolism (primarily CYP3A3/4) can be inhibited by certain enzyme inhibitors, yielding increases in serum carbamazepine concentrations and carbamazepine intoxication** (Table 39-5 and Figure 39-1, top). Autoinduction makes carbamazepine particularly vulnerable to the effects of enzyme inhibitors. Thus, a variety of agents that inhibit CYP3A3/4 can yield increased serum carbamazepine concentrations and side effects (Table 39-5 and Figure 39-1, top). Particularly noteworthy are the calcium channel blockers diltiazem and verapamil (but not nimodipine or nifedipine) and all of the erythromycin-like antibiotics.

3. **Carbamazepine has an active epoxide (carbamazepine-E) metabolite** (Figure 39-1, top). Valproate inhibits epoxide hydrolase, yielding increased serum carbamazepine-E (but not carbamazepine) concentrations (Table 39-5). Free carbamazepine may also increase because of valproate-induced displacement of carbamazepine protein binding.

TABLE 39-4. Selected drugs whose serum concentrations are DECREASED by carbamazepine (and oxcarbazepine)

Antidepressants	Anticonvulsants	Dihydropyridine CCBs
Bupropion	Carbamazepine	*Felodipine*
Citalopram	Ethosuximide	Nimodipine
Mirtazapine	Felbamate	

Note. Italic type indicates that serum concentrations of the medication may decrease to a clinically significant extent not only with carbamazepine but also with oxcarbazepine, hindering the efficacy of the agent. (?) = unclear clinical significance; CCBs = calcium channel blockers.

Sertraline
Tricyclics

Antipsychotics
Aripiprazole
Brexpiprazole
Cariprazine
Chlorpromazine (?)
Clozapine
Fluphenazine (?)
Haloperidol
Lumateperone
Olanzapine
Quetiapine (?)
Risperidone
Thiothixene (?)
Ziprasidone (?)

Anxiolytics/sedatives
Alprazolam (?)
Buspirone
Clonazepam
Eszopiclone (?)
Midazolam

Anticoagulant
Warfarin

Lamotrigine
Levetiracetam (?)
Oxcarbazepine
Phenytoin
Primidone
Tiagabine
Topiramate
Valproate
Zonisamide

Analgesics
Alfentanil
Buprenorphine
Fentanyl (?)
Levobupivacaine
Methadone
Tramadol

Stimulants
Methylphenidate
Modafinil

Anti-infectives
Caspofungin
Delavirdine
Doxycycline
Praziquantel
Protease inhibitors

Immunosuppressants
Cyclosporine (?)
Sirolimus
Tacrolimus

Muscle relaxants
Atracurium
Cisatracurium
Doxacurium
Mivacurium
Pancuronium
Pipercuronium
Rocuronium
Vecuronium

Steroids
Dexamethasone
Hormonal contraceptives
Mifepristone
Prednisolone

Others
Paclitaxel
Quinidine
Repaglinide
Theophylline (?)
Thyroid hormones

Note. Italic type indicates that serum concentrations of the medication may decrease to a clinically significant extent not only with carbamazepine but also with oxcarbazepine, hindering the efficacy of the agent. (?) = unclear clinical significance; CCBs = calcium channel blockers.

TABLE 39-5. **Selected drugs that INCREASE serum concentrations of carbamazepine (but not oxcarbazepine)**

Antidepressants
Fluoxetine
Fluvoxamine
Nefazodone

Anti-infectives
Isoniazid
Quinupristin/dalfopristin

Azole antifungals
Fluconazole
Itraconazole
Ketoconazole

Macrolide antibiotics
Clarithromycin
Erythromycin
Troleandomycin

Calcium channel blockers
Diltiazem
Verapamil

Hypolipidemics
Gemfibrozil
Nicotinamide

Others
Acetazolamide
Cimetidine
Danazol
Grapefruit juice
Omeprazole
d-Propoxyphene
Ritonavir
Ticlopidine (?)
Valproate (increases CBZ-E)

Note. (?) = unclear clinical significance; CBZ-E = carbamazepine-10,11-epoxide.

Carbamazepine has a wide variety of pharmacokinetic drug-drug interactions, in excess of and different from those seen with lithium or valproate. In the following subsections, we review carbamazepine drug interactions with other medications, with agents of particular interest in the management of mood disorders indicated in **boldface** type. The reader interested in detailed reviews of carbamazepine drug-drug interactions is referred to the review by Ketter *et al.* (1991a, 1991b).

Interactions With Mood Stabilizers and Anticonvulsants

The combination of carbamazepine and lithium is frequently used in bipolar disorder, and it may provide additive or synergistic antimanic (Kramlinger and Post 1989a) and antidepressant (Kramlinger and Post 1989b) effects. This combination is generally well tolerated, with merely additive (as opposed to synergistic or antagonistic) neurotoxicity (McGinness *et al.* 1990), which can be minimized by gradual dosage escalation. Pharmacokinetic interactions between these drugs do not occur because lithium has no hepatic metabolism. Adverse effects of lithium and carbamazepine can be either additive or complementary. Combination therapy decreases the serum concentrations of thyroid hormones in an additive fashion (Kramlinger and Post 1990), whereas lithium-induced increases in leukocytes and neutrophils based on increases in colony-stimulating factor override the common benign decreases in these indices seen with carbamazepine based on suppression of colony-stimulating factor (Kramlinger and Post 1990). It is important to note, however, that lithium cannot alter the course of the rare severe bone marrow suppression caused by carbamazepine (Joffe and Post 1989). In addition, the diuretic effect of lithium overrides the antidiuretic effect of carbamazepine (Klein 1987). Thus, carbamazepine will not reverse lithium-induced diabetes insipidus, although lithium is useful in attenuating carbamazepine-induced hyponatremia (Klein 1987; Vieweg *et al.* 1987). Whether it would also do this for oxcarbazepine, which is even more commonly associated with hyponatremia, is not known.

Reports suggest that the combination of carbamazepine plus **valproate** is not only tolerated but also shows psychotropic synergy (Keck *et al.* 1992; Ketter *et al.* 1992; Tohen *et al.* 1994). Effective combination treatment with these two medications requires knowledge of their drug interactions, which can be simplified with the general principle that usual dosages of carbamazepine should be reduced. Valproate inhibits carbamazepine metabolism (Macphee *et al.* 1988) and displaces carbamazepine from plasma proteins, increasing the free carbamazepine fraction that is active and available to be metabolized (Macphee *et al.* 1988; Moreland *et al.* 1984). Valproate inhibits epoxide hydrolase, increasing the serum carbamazepine-E concentration, which could increase effectiveness or side effects covertly because the increases in carbamazepine-E would not be measured in carbamazepine assays (Brodie *et al.* 1983; Kutt *et al.* 1985; Rambeck *et al.* 1987).

These interactions can potentially confuse clinicians, because patients can experience neurotoxicity from elevated serum carbamazepine-E or free carbamazepine concentrations even if their serum total carbamazepine concentrations are at therapeutic levels (Kutt *et al.* 1985). Carbamazepine decreases serum valproate concentrations (Kondo *et al.* 1990) but increases the formation of the active valproic acid metabolite, 2-propyl-4-pentenoic acid (4-ene-valproic acid [Kondo *et al.* 1990]), which may be hepatotoxic and may add to teratogenicity (Nau and Loscher 1986; Scheffner *et al.* 1988). The risk of fatal hepatitis is of great concern for infants treated with combinations of valproate with other anticonvulsants (Scheffner *et al.* 1988), but this risk is much lower in adults (Dreifuss *et al.* 1989). As a general rule, clinicians should clinically monitor patients receiving the carbamazepine-valproate combination for adverse effects, and they should consider decreasing the carbamazepine dosage in advance of adding valproate and possibly increasing the valproate dosage if needed.

Carbamazepine increases **lamotrigine** metabolism and approximately halves blood lamotrigine concentrations. Thus, lamotrigine dosages can be doubled with this combination.

Carbamazepine induces the metabolism of **carbamazepine** (autoinduction) and **oxcarbazepine** (McKee *et al.* 1994) as well as several older (e.g., ethosuximide, phenytoin, primidone) and newer (e.g., felbamate, **topiramate**) anticonvulsants (Sachdeo *et al.* 1996), tiagabine (Samara *et al.* 1998), and **zonisamide** (Ojemann *et al.* 1986), but not gabapentin (Radulovic *et al.* 1994) or pregabalin (Brodie *et al.* 2005). The enzyme-inducing anticonvulsants phenytoin, phenobarbital, primidone, methsuximide, and felbamate decrease serum carbamazepine levels.

Interactions With Antidepressants

Antidepressants are commonly combined with mood stabilizers in the treatment of bipolar disorder. These drug-drug interactions may be bidirectional.

Fluoxetine (Grimsley *et al.* 1991; Pearson 1990), **fluvoxamine** (Fritze *et al.* 1991), and **nefazodone** (Ashton and Wolin 1996; Laroudie *et al.* 2000; Roth and Bertschy 2001) have been reported to inhibit carbamazepine metabolism, causing increased

carbamazepine concentrations and toxicity. In addition, parkinsonian symptoms have been reported after adding fluoxetine to carbamazepine (Gernaat *et al.* 1991). In contrast, sertraline (Rapeport *et al.* 1996), paroxetine (Andersen *et al.* 1991), citalopram (Moller *et al.* 2001), and mirtazapine (Sitsen *et al.* 2001) do not appear to alter carbamazepine metabolism. Carbamazepine seems to decrease serum concentrations of racemic **citalopram** and **escitalopram** (Steinacher *et al.* 2002). Carbamazepine also appears to induce the metabolism of **mirtazapine** (Sitsen *et al.* 2001), **mianserin** (Eap *et al.* 1999), **sertraline** (Khan *et al.* 2000; Pihlsgard and Eliasson 2002), and (to some extent) trazodone (Otani *et al.* 1996), as well as (most likely) vilazodone (Novartis Pharmaceuticals 2015).

Patients receiving carbamazepine and **bupropion** have low serum bupropion concentrations and high hydroxybupropion (metabolite) concentrations (Ketter *et al.* 1995a), but this is unlikely to be clinically problematic because hydroxybupropion is active. Carbamazepine appears to induce the metabolism of tricyclic antidepressants, including amitriptyline.

Carbamazepine may increase rather than decrease serum levels of transdermal selegiline and its metabolites (Novartis Pharmaceuticals 2015). Theoretical grounds have been stated for concern about combining carbamazepine with monoamine oxidase inhibitors (Thweatt 1986), but case reports (Joffe *et al.* 1985; Yatham *et al.* 1990) and series (Ketter *et al.* 1995b) suggest that the addition of phenelzine or tranylcypromine to carbamazepine may be well tolerated. However, the antituberculosis drug isoniazid, which is also a monoamine oxidase inhibitor, increases carbamazepine levels.

Interactions With Antipsychotics

Combinations of antipsychotics with mood stabilizers are commonly required in severe mania (American Psychiatric Association 2002) and are increasingly used in bipolar maintenance treatment (Ketter 2015; Novartis Pharmaceuticals 2015).

Carbamazepine increases **haloperidol** metabolism (Ereshefsky *et al.* 1986; Jann *et al.* 1989; Kahn *et al.* 1990), dramatically lowering its blood concentrations. However, clinical responses with this combination can be unaffected or even improved (Jann *et al.* 1989; Kahn *et al.* 1990). Weaker evidence suggests that carbamazepine may increase the metabolism of other first-generation antipsychotic agents, including fluphenazine (Ereshefsky *et al.* 1986; Jann *et al.* 1989), chlorpromazine (Raitasuo *et al.* 1994), and thiothixene (Ereshefsky *et al.* 1986), but not thioridazine (Tiihonen *et al.* 1995), and that loxapine, chlorpromazine, and amoxapine may increase carbamazepine-E concentrations (Pitterle and Collins 1988). In view of these interactions, serum antipsychotic medication concentrations should be checked if patients' symptoms do not respond to standard dosages of antipsychotic agents during combined therapy with carbamazepine.

Coadministration of **clozapine** with carbamazepine is not recommended in view of the potential for synergistic bone marrow suppression (Novartis Pharmaceuticals 2015). European centers that have used this drug combination report that carbamazepine decreases clozapine concentrations (Raitasuo *et al.* 1993). Thus, clinicians considering the adjunctive use of a psychotropic anticonvulsant with clozapine should prescribe valproate or another anticonvulsant rather than carbamazepine, except under unusual circumstances.

Carbamazepine increases the metabolism of **olanzapine** (Linnet and Olesen 2002; Lucas *et al.* 1998), **risperidone** (Ono *et al.* 2002; Spina *et al.* 2000; Yatham *et al.* 2003),

quetiapine (Grimm *et al.* 2006), **aripiprazole** (Novartis Pharmaceuticals 2015), **ziprasidone** (Miceli *et al.* 2000), and possibly lurasidone, brexpiprazole, cariprazine, and lumateperone; therefore, dosages of these atypical antipsychotics may need to be increased (Tohen *et al.* 2008; Yatham *et al.* 2003).

Interactions With Anxiolytics and Sedatives

Carbamazepine is commonly coadministered with **benzodiazepines**, with merely additive CNS adverse effects (e.g., sedation, ataxia). Carbamazepine may decrease serum levels of clonazepam (Lai *et al.* 1978; Yukawa *et al.* 2001), alprazolam (Arana *et al.* 1988; Furukori *et al.* 1998), clobazam (Levy *et al.* 1983), and midazolam (Backman *et al.* 1996), potentially decreasing the efficacy of these agents. The newer hypnotics eszopiclone and zolpidem, which are susceptible to drug interactions involving induction of CYP3A4, may have drug interactions with carbamazepine (Drover 2004). Of interest, carbamazepine may be effective in ameliorating benzodiazepine withdrawal symptoms (Ries *et al.* 1989).

Interactions With Stimulants

Armodafinil and carbamazepine combination treatment may decrease armodafinil levels by 37% and carbamazepine levels by 25% (Darwish *et al.* 2015).

Interactions With Calcium Channel Blockers

Of clear clinical importance, elevated serum carbamazepine concentrations and neurotoxic effects have been reported during concurrent treatment with the nondihydropyridines **verapamil** and **diltiazem** but not with the dihydropyridines nifedipine (Brodie and MacPhee 1986; Price and DiMarzio 1988) and nimodipine. These observations are consistent with the finding that verapamil and diltiazem, but not nifedipine, inhibit the hepatic oxidative metabolism of various drugs (Hunt *et al.* 1989). Enzyme-inducing anticonvulsants like carbamazepine appear to decrease serum concentrations of **dihydropyridines** such as nimodipine (Tartara *et al.* 1991) and felodipine (Capewell *et al.* 1988; Zaccara *et al.* 1993).

Interactions With Substances of Abuse

Ethanol and carbamazepine do not interact pharmacokinetically (Dar *et al.* 1989; Pynnonen *et al.* 1978). However, carbamazepine attenuates alcohol withdrawal symptoms (Malcolm *et al.* 1989). Disulfiram combined with carbamazepine is well tolerated and does not cause clinically significant changes in serum carbamazepine and carbamazepine-E concentrations (Krag *et al.* 1981). Cigarette smoking does not alter carbamazepine metabolism (Bachmann *et al.* 1990), and carbamazepine does not alter caffeine pharmacokinetics (Wietholtz *et al.* 1989).

Interactions With Nonpsychotropic Drugs

Carbamazepine induces the metabolism of diverse medications, raising the possibility of undermining the efficacy of **steroids** (contraceptives, dexamethasone, mifepristone), **methylxanthines** (theophylline, aminophylline), antibiotics (**doxycycline**), **protease inhibitors**, **neuromuscular blockers** (pancuronium, vecuronium, doxacurium), analgesics (**methadone**), **immunosuppressants** (sirolimus, tacrolimus), the anticoagulant **warfarin**, and possibly dicumarol (see Table 39-4). For women taking carbamazepine, dosages of oral contraceptive preparations may need to be adjusted to ensure continued efficacy (Crawford 2002).

Similarly, a variety of medications can increase serum carbamazepine concentrations and cause clinical toxicity. Such medications include **isoniazid**, **azole antifungals** (ketoconazole), **macrolide antibiotics** (erythromycin and clarithromycin), **protease inhibitors** (ritonavir and nelfinavir), **hypolipidemics** (gemfibrozil and nicotinamide), and the carbonic anhydrase inhibitor **acetazolamide** (see Table 39-5). In addition, other medications such as cisplatin and doxorubicin may decrease serum carbamazepine levels, potentially leading to inefficacy.

Oxcarbazepine

Compared with carbamazepine, oxcarbazepine has fewer clinically significant drug-drug interactions. Differences in three major areas seem to contribute importantly to differences between oxcarbazepine and carbamazepine with regard to drug-drug interactions.

1. **Oxcarbazepine is only a modest to moderate enzyme (CYP3A4) inducer, which yields clinically significant decreases in serum concentrations of some medications** (see Table 39-4). Oxcarbazepine yields minor enzyme heteroinduction (but not autoinduction), which is clearly less robust than that seen with carbamazepine, but the effect may be clinically significant for some medications (in *italics* in Table 39-4).
2. **Oxcarbazepine metabolism (which is primarily by arylketone reductase) is not generally susceptible to enzyme inhibitors.** The absence of autoinduction and the robust actions of cytosol reductases that mediate conversion to MHD

appear to render oxcarbazepine metabolism not susceptible to the common phenomenon of inhibition by other agents seen with carbamazepine. Thus, the medications listed in Table 39-5 that can elevate serum carbamazepine concentrations and cause neurotoxicity do not appear to have such interactions with oxcarbazepine.

3. **Oxcarbazepine has an active (MHD) metabolite** (see Figure 39-1, bottom middle). MHD metabolism, unlike carbamazepine-E catabolism, is not inhibited by valproate, presumably because of the lack of involvement of epoxide hydrolase in MHD disposition. Thus, coadministration of valproate with oxcarbazepine does not result in toxicity related to increased MHD.

Interactions With Mood Stabilizers and Anticonvulsants

Oxcarbazepine, in contrast with carbamazepine, does not induce valproate metabolism and seems to have less robust effects on **lamotrigine** metabolism (May *et al.* 1999). Oxcarbazepine may modestly decrease serum concentrations of topiramate (May *et al.* 2002) and levetiracetam (May *et al.* 2003). In addition, oxcarbazepine can increase serum phenytoin concentrations, presumably by inhibiting CYP2C19 activity. The anticonvulsants phenytoin, phenobarbital, primidone, and carbamazepine may induce oxcarbazepine metabolism, yielding decreased serum MHD concentrations (McKee *et al.* 1994).

Interactions With Antidepressants

Oxcarbazepine, in contrast with carbamazepine, does not robustly induce citalopram metabolism.

Interactions With Antipsychotics

Oxcarbazepine, unlike carbamazepine, does not robustly induce antipsychotic metabolism.

Interactions With Anxiolytics and Sedatives

Oxcarbazepine may decrease serum concentrations of **benzodiazepines**.

Interactions With Calcium Channel Blockers

Oxcarbazepine appears to decrease serum concentrations of **dihydropyridine** calcium channel blockers (which are CYP3A4 substrates) to some extent.

Interactions With Nonpsychotropic Drugs

Oxcarbazepine, compared with carbamazepine, also seems to have fewer interactions with nonpsychotropic drugs. Thus, neither the CYP3A4 inhibitor erythromycin (Keranen *et al.* 1992a) nor the heteroinhibitor cimetidine (Keranen *et al.* 1992b) appears to alter oxcarbazepine pharmacokinetics in healthy volunteers.

However, oxcarbazepine seems to have a clinically significant interaction with **hormonal contraceptives**. In healthy female volunteers, oxcarbazepine appeared to decrease ethinylestradiol and levonorgestrel derived from hormonal contraceptives by as much as 50% (Fattore *et al.* 1999; Kramer *et al.* 1992), such that use of higher-dosage forms of estrogen-related oral contraceptives may be indicated.

Like carbamazepine, oxcarbazepine may decrease serum concentrations of the analgesic buprenorphine, the anticancer agent paclitaxel, and the antidiabetic agent repaglinide. Oxcarbazepine also yields decreases in serum concentrations of the dihydropyridine calcium channel blocker felodipine, which is also a CYP3A4 substrate. In contrast with carbamazepine, the CYP3A4 inhibitor erythromycin and the antidepressant viloxazine do not yield clinically significant increases in serum oxcarbazepine concentrations.

Eslicarbazepine Acetate

Eslicarbazepine acetate, which shares the same active metabolite as oxcarbazepine, also has fewer clinically significant drug-drug interactions compared with carbamazepine. Eslicarbazepine acetate is modestly protein bound, without significant related interactions. This drug does not have significant effects on most CYP enzyme pathways, including CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP4A9/11 (Almeida and Soares-da-Silva 2007). Its three main pharmacokinetic effects are weak induction of CYP3A4, weak induction of uridine 5'-diphosphoglucuronosyltransferases, and weak inhibition of CYP2C19 (Zaccara *et al.* 2015).

Interactions With Mood Stabilizers

Similar to oxcarbazepine and in contrast with carbamazepine, eslicarbazepine acetate does not significantly induce valproate metabolism. Moreover, eslicarbazepine acetate does not have significant interactions with lamotrigine or topiramate metabolism (Bialer and Soares-da-Silva 2012).

Interactions With Nonpsychotropic Drugs

Because of its modest induction of CYP3A4 activity, eslicarbazepine acetate may induce moderate reductions in estradiol (up to 42%) in a possibly dose-dependent interaction, potentially reducing the effectiveness of oral contraceptives (Bialer and Soares-da-Silva 2012). Simvastatin levels may be decreased by up to 40% with eslicarbazepine acetate coadministration, presumably as a function of CYP3A4 induction (Zaccara *et al.* 2015).

Practical Clinical Principles for Use of Carbamazepine and Oxcarbazepine

Because blood levels of carbamazepine do not correlate with the degree of clinical response to carbamazepine in either mood disorders (Post *et al.* 2007) or epilepsy, and blood levels associated with toxicity vary widely among patients (Tomson 1984), upward titration of the carbamazepine dose should proceed slowly to minimize side effects and maximize effectiveness. That is, dose titration can be accomplished with minimal blood level monitoring.

There are now long-acting preparations of both carbamazepine (Equetro and Carbatrol) and oxcarbazepine (Oxtellar). Clinical studies in patients with mood disorders, as opposed to epilepsy, support the use of single nighttime doses to maximize effects on sleep and minimize daytime side effects. This approach also simplifies the regimen and enhances compliance.

Conclusion

Because of the past lack of an FDA indication, complexity of use, and methodological concerns regarding earlier efficacy studies, carbamazepine was generally considered an alternative rather than a first-line intervention in bipolar disorder. However, the approval of a proprietary carbamazepine beaded extended-release capsule formulation (Equetro) for the treatment of acute manic and mixed episodes in patients with bipolar disorder and the low propensity of carbamazepine to cause the weight gain and metabolic problems seen with some other agents may lead clinicians to reassess the role of this agent in the management of bipolar disorder (Ketter 2015).

Oxcarbazepine has more limited evidence of efficacy in bipolar disorder compared with carbamazepine, but it has good tolerability (except for an increased incidence of hyponatremia) and fewer drug-drug interactions. Some data suggest that oxcarbazepine is less effective than carbamazepine in severe or psychotic mania. MHD (the active metabolite of oxcarbazepine) and eslicarbazepine acetate (the prodrug to the *S*-enantiomer of MHD) likewise have enhanced tolerability and fewer drug-drug interactions, but their efficacy in bipolar disorder remains to be established.

With carbamazepine but not oxcarbazepine, common benign leukopenia (which can be reversed with lithium) may occur and must be distinguished from rare serious aplastic anemia. Physicians and caregivers must alert patients to symptoms of this adverse effect (e.g., fever, sore throat, petechiae) so that a complete blood count can be performed rapidly. In addition, carbamazepine--and to a lesser extent, oxcarbazepine--in combination therapy induces the metabolism of other drugs, especially the atypical antipsychotics, which suggests that dosages may need to be increased accordingly. Other commonly used drugs (e.g., erythromycin, verapamil) can inhibit carbamazepine (but not oxcarbazepine) metabolism, causing carbamazepine toxicity. Instructing patients to alert their other caregivers and their pharmacist that they are receiving carbamazepine may help avoid drug interactions.

Carbamazepine is an important treatment option for patients with bipolar disorder who experience an inadequate response or unacceptable adverse effects with lithium and valproate. Awareness of carbamazepine and oxcarbazepine pharmacology and potential drug-drug interactions will enable clinicians to provide the safest and most effective care for their patients with bipolar disorder.

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CHAPTER 40

Gabapentin and Pregabalin

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In this chapter we review background information, pharmacological profiles, clinical indications, adverse events, and other considerations for two anticonvulsant agents, gabapentin and pregabalin.

Gabapentin

Early observations of enhanced general well-being in patients with epilepsy treated with anticonvulsants, as well as various early hypotheses of kindling and sensitization proposed as models of affective illness progression (Weiss and Post 1998), have promoted controlled investigations of anticonvulsant drugs as potential mood-stabilizing agents.

Gabapentin is FDA approved for the adjunctive treatment of complex partial epilepsy in pediatric patients ages 3-12 years and individuals older than 12 years (with and without secondary generalization) and for the management of postherpetic neuralgia in adults. A retrospective review of five placebo-controlled trials of gabapentin in more than 700 patients with refractory partial seizure disorder additionally supported the concept of improvement in general well-being, prompting controlled investigation of the drug in primary psychiatric conditions (Dimond *et al.* 1996).

Structure-Activity Relations

Gabapentin (2-[1-(aminomethyl)cyclohexyl]acetic acid) is a synthetic analog of GABA (Figure 40-1).

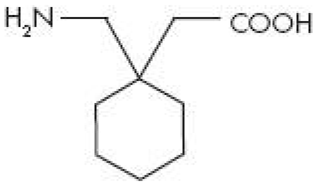

FIGURE 40-1. Chemical structure of gabapentin.

Pharmacological Profile and Mechanism of Action

The mechanism of gabapentin's anticonvulsant and psychotropic action is not fully understood. Gabapentin was originally developed as a GABA analog. As reviewed by Taylor *et al.* (1998), GABA is the major inhibitory neurotransmitter in the cerebral cortex. Preclinical studies have suggested that gabapentin increases brain and intracellular GABA by an amino acid active transporter at the blood-brain barrier and multiple enzymatic regulatory mechanisms, respectively. In vitro, gabapentin increases the activity of glutamic acid decarboxylase, the enzyme that converts glutamate to GABA (Taylor *et al.* 1992). Conversely, gabapentin has been shown to inhibit GABA transaminase, the enzyme primarily responsible for GABA catabolism (Loscher *et al.* 1991). Glutamate metabolism is also modulated by gabapentin. In vitro, gabapentin inhibits branched-chain amino acid aminotransferase, which is responsible for glutamate synthesis (Hutson *et al.* 1998); gabapentin also activates glutamate dehydrogenase, which is involved in glutamate catabolism (Goldlust *et al.* 1995).

These enzymatic regulatory mechanisms that suggest increased synthesis and decreased degradation of GABA are clinically relevant. Several but not all studies have reported decreased levels of cerebrospinal fluid (Goddard *et al.* 1996; Gold *et al.* 1980; Roy *et al.* 1991), plasma (Petty *et al.* 1990), and magnetic resonance spectroscopic GABA (Sanacora *et al.* 1999) in patients with affective illness compared with healthy control subjects. Furthermore, increased magnetic resonance spectroscopic occipital GABA concentrations have been reported with serotonin reuptake inhibitor treatment in patients with depression (Sanacora *et al.* 2002) and gabapentin treatment in patients with complex partial epilepsy (Petroff *et al.* 1996).

Gabapentin also has been shown to bind to the a_2 subunit receptor of brain voltage-dependent calcium channels, an effect that may relate to the subsequent inhibition of monoaminergic transmission (Schlicker *et al.* 1985). There is no known direct activity at dopamine, serotonin, benzodiazepine, or histamine receptors. However, gabapentin has been reported to increase whole-blood levels of serotonin in healthy control subjects (Rao *et al.* 1988).

Formulations

Gabapentin is available in multiple dosage forms, including oral capsules (100, 300, and 400 mg), tablets (100, 300, 400, 600, and 800 mg), and an oral solution (250 mg/5 mL), and generic equivalent products are available (Pfizer 2017). For patients who cannot ingest capsules or tablets, the capsule products may be opened and sprinkled on food. A gabapentin enacarbil oral extended-release tablet (300 and 600 mg) is also available in the United States (Arbor Pharmaceuticals 2020). The FDA-approved indications for this product include treatment, in adults, of moderate to severe primary restless legs syndrome and management of postherpetic neuralgia (Arbor Pharmaceuticals 2020).

Pharmacokinetics and Disposition

All bioavailability, distribution, and elimination parameters are based on the gabapentin molecule itself, as there is no active metabolite. Gabapentin exhibits nonlinear bioavailability most likely related to an active saturable

L-amino acid transport carrier present in the gut and blood-brain barrier (McLean 1999). Gabapentin may be taken without regard to mealtimes, as food does not significantly affect the rate or extent of absorption. The alternative enacarbil formulation produces more consistent absorption and/or transport in the gastrointestinal tract, and this formulation should be administered with food, which enhances absorption (Arbor Pharmaceuticals 2020). There is no evidence of plasma protein binding, hepatic metabolism, or cytochrome P450 (CYP) autoinduction. The elimination half-life is 6-8 hours, with a recommended three-times-a-day dosing strategy. Gabapentin is eliminated from the systemic circulation unchanged by renal excretion. Patients with compromised renal function will show evidence of reduced gabapentin clearance.

Indications and Efficacy

Epilepsy

Gabapentin currently is FDA approved for use in the adjunctive treatment of partial seizures with and without secondary generalization in adults and pediatric patients 3 years and older with epilepsy (Pfizer 2017). Approval for this indication was based on controlled evaluations of gabapentin at daily dosages of 600-1,800 mg. Additional research has reported efficacy and tolerability for gabapentin monotherapy at daily dosages up to 4,800 mg in patients with refractory epilepsy (Beydoun *et al.* 1998). There is no established therapeutic plasma level for seizure control. Gabapentin has a highly favorable side-effect profile, with only mild side effects (sedation, dizziness, and ataxia) commonly reported.

Nonepilepsy Neurological Conditions

Neuropathic pain. Gabapentin received FDA approval for use in the management of postherpetic neuralgia in adults on the basis of two placebo-controlled studies (Rice *et al.* 2001; Rowbotham *et al.* 1998). Gabapentin also has been systematically evaluated in diabetic neuropathy (Backonja *et al.* 1998).

The initial postherpetic neuralgia (Rowbotham *et al.* 1998) and diabetic neuropathy (Backonja *et al.* 1998) studies were randomized, double-blind, placebo-controlled, parallel-group multicenter investigations with three phases of evaluation. The first phase identified the subject population, which comprised patients with a diabetic neuropathy duration of 1-5 years (Backonja *et al.* 1998) or postherpetic neuralgia duration of 3 months (Rowbotham *et al.* 1998). The 8-week double-blind phases consisted of a 4-week step titration (900, 1,800, 2,400, and 3,600 mg/day for weeks 1-4, respectively) and a 4-week fixed-dosage period wherein the dosage that was effective and tolerable from the titration phase was held constant. There were no differences in demographics or rates of dropout due to inefficacy or adverse events between the gabapentin group and the placebo group.

Among the 229 patients with postherpetic neuralgia (Rowbotham *et al.* 1998), greater pain reduction occurred with gabapentin, which was noted as early as week 2 and maintained throughout the entire study period. Similarly, secondary measures of mood, such as depression, anger/hostility, fatigue/inertia, and physical functioning, were treated more effectively with gabapentin than with placebo. Improvement was maintained for 83% of patients receiving gabapentin 2,400 mg/day and for 65% of individuals taking 3,600 mg/day.

Among the 165 patients with diabetic neuropathy (Backonja *et al.* 1998), greater pain reduction (as measured with an 11-point Likert scale) occurred with gabapentin than with placebo. This difference was statistically significant as early as week 2 of the blind titration phase and remained significant for the duration of the 8-week study. Significant reductions in sleep interference related to pain as well as improved quality of life were also reported. Gabapentin appeared to be well tolerated, with improvement for 67% of the patient group continued on a maximum daily dosage of 3,600 mg.

Finally, a 7-week placebo-controlled study evaluated gabapentin (1,800 or 2,400 mg/day in three divided doses) in 334 patients with postherpetic neuralgia (Rice *et al.* 2001). Pain was significantly reduced with both gabapentin dosages, with similar improvements in sleep. An improvement in pain score was noted as early as week 1 and was maintained throughout the study.

These results contrast with findings of additional studies that have investigated gabapentin's utility in the management of perioperative pain (Zhang *et al.* 2015). In a reanalysis of two randomized controlled trials of adjunctive gabapentin versus adjunctive placebo in patients undergoing total knee (*n* = 102) or total hip arthroplasty (*n* = 101), gabapentin did not significantly reduce the primary outcome measure of morphine consumption immediately postprocedure and 24, 48, and 72 hours postsurgery.

Movement disorders (off-label). Controlled investigations of gabapentin have been conducted in several movement disorders. These studies were much smaller than the neuropathic pain studies mentioned in the prior section but included amyotrophic lateral sclerosis (Miller *et al.* 1996), essential tremor (Ondo *et al.* 2000; Pahwa *et al.* 1998), and parkinsonism (Olson *et al.* 1997).

In a study of 152 patients with amyotrophic lateral sclerosis, participants were randomly assigned to gabapentin 2,400 mg/day or placebo for 6 months. Decline in muscle strength, the primary outcome measure, occurred more slowly in the gabapentin-treated patients than in the placebo-treated patients (Miller *et al.* 1996).

Controlled studies of gabapentin for essential tremor have reported mixed results. The first controlled study lasted 2 weeks and showed no difference between gabapentin 1,800 mg/day and placebo for treatment of essential tremor (Pahwa *et al.* 1998). A second controlled study, a 6-week evaluation of two gabapentin dosages (1,800 and 3,600 mg/day) in patients with essential tremor, demonstrated significantly greater improvements in self-report scores, observed tremor scores, and activities of daily living scores for individuals randomly assigned to gabapentin compared with placebo (Ondo *et al.* 2000).

In a 1-month double-blind, placebo-controlled evaluation of gabapentin in 19 patients with advanced parkinsonism, gabapentin at a mean total dosage of 1,200 mg/day was superior to placebo in reducing rigidity, bradykinesia, and tremor, as measured by the Unified Parkinson's Disease

Rating Scale (Olson *et al.* 1997). The improvements in rigidity and bradykinesia were independent of tremor improvement.

Finally, trials have shown positive results for gabapentin in the treatment of restless legs syndrome, particularly with the proprietary enacarbil formulation at dosages of 300-1,200 mg/day (Yaltho and Ondo 2010).

Migraine headache (off-label) Comorbid migraine headache and bipolar disorder is highly prevalent and clinically significant (Mahmood *et al.* 1999). Because of their mood-stabilizing effects and migraine prophylactic properties, anticonvulsants seem to be ideal in this patient population. Mathew *et al.* (2001) suggested that gabapentin is an effective agent for migraine prophylaxis. This three-phase controlled evaluation of gabapentin included 143 patients with migraine (with and without aura). Phase 1 was a 4-week single-blind placebo period during which baseline migraine headache frequency was established. Phase 2 was a 4-week double-blind, placebo-controlled, flexible-dosage titration period during which patients received gabapentin at dosages up to 2,400 mg/day. Phase 3 was an 8-week double-blind, placebo-controlled period during which the dosage of gabapentin was held constant. Patients randomly assigned to gabapentin 2,400 mg/day had significantly greater reductions in migraine attacks compared with placebo-treated patients. Dropout rates were higher with gabapentin and were primarily related to drowsiness and somnolence.

Psychiatric Disorders

Gabapentin is commonly used off-label for psychiatric disorders. This use is seen more commonly in primary care than in psychiatry settings (Costales and Goodin 2021), with patients also using antidepressants, benzodiazepines, and opioids.

Anxiety disorders (off-label). Gabapentin produces a dose-dependent anxiolytic response in animal models (Singh *et al.* 1996). Open-trial investigations have reported positive results with add-on gabapentin in the treatment of generalized anxiety disorder (Pollack *et al.* 1998), panic disorder (Pollack *et al.* 1998), and refractory OCD (Cora-Locatelli *et al.* 1998). Findings from controlled investigations of gabapentin in social anxiety disorder (i.e., DSM-IV social phobia) (Pande *et al.* 1999) and panic disorder (Pande *et al.* 2000b) suggested that gabapentin has anxiolytic activity.

Pande *et al.* (1999) conducted a 14-week randomized, double-blind, placebo-controlled, two-site study of 69 outpatients with DSM-IV-confirmed social phobia (American Psychiatric Association 1994). All patients were required to have a score of 50 or greater on the Liebowitz Social Anxiety Scale (LSAS) at baseline. Reductions in LSAS scores served as the primary outcome measure. In the intent-to-treat analysis, gabapentin was more effective than placebo in reducing social anxiety symptoms. The dosage range for gabapentin was 900-3,600 mg/day, and 56% of patients reported symptom response and tolerability with the maximum daily dosage of 3,600 mg. Dizziness and dry mouth were significantly more common in patients treated with gabapentin.

The second study was an 8-week randomized, placebo-controlled, six-site monotherapy study of 103 patients with DSM-IV-confirmed panic disorder with or without agoraphobia (Pande *et al.* 2000b). Gabapentin was dosed flexibly between 600 and 3,600 mg/day. The primary outcome measure was a decrease in Panic and Agoraphobia Scale (PAS) score. There were no differences in dropout rates between the gabapentin and placebo groups. In the intent-to-treat analysis, no difference in PAS score reduction was seen between patients randomly assigned to gabapentin and those receiving placebo. In a post hoc stratification of high ([?] 20) and low (< 20) PAS symptom severity, patients with high symptom severity who were randomly assigned to gabapentin had a greater decrease in PAS score from baseline to endpoint than did those who received placebo. Somnolence, headache, dizziness, infection, asthenia, and ataxia were more common with gabapentin than with placebo.

Bipolar disorder (off-label). Numerous case reports on and open trials of gabapentin as a mood stabilizer--encompassing more than 400 patients with a pooled response rate between 65% and 70%--have been reviewed elsewhere (Frye *et al.* 2000; Yatham *et al.* 2002).

One double-blind, placebo-controlled outpatient study evaluated add-on gabapentin for the treatment of bipolar I disorder with manic, hypomanic, or mixed symptoms (Pande *et al.* 2000a). The first phase of the study involved a 2-week single-blind placebo lead-in wherein dosages of the patient's primary mood stabilizer (lithium or valproate) could be adjusted to maximal clinical benefit and a minimum threshold of therapeutic level (i.e., lithium 0.5 mmol/L, valproate > 50 mg/mL). The second phase was a 10-week double-blind trial in which participants were randomly assigned to gabapentin at flexible dosages between 600 and 3,600 mg/day (taken in three divided doses) or to placebo. In the intent-to-treat population, 117 subjects were randomly assigned to treatment; no differences in demographic profile or dropout rate were found between the two groups. The primary outcome measure (total decrease in score on the Young Mania Rating Scale) was significantly different between groups in favor of add-on placebo. In a post hoc analysis, it was observed that lithium adjustments in the single-blind placebo lead-in phase were made more frequently in the placebo group than in the gabapentin group; most of these adjustments (9 of 12 [75%]) consisted of a dosage increase. This fact suggests either a strong placebo response or the effect of maximizing lithium blood levels to achieve a greater antimanic response. Of the gabapentin-treated patients who had drug levels measured, nearly 20% had plasma gabapentin levels that were undetectable.

The second controlled study was a 6-week double-blind, placebo-controlled crossover comparative trial of gabapentin monotherapy, lamotrigine monotherapy, and placebo in 35 inpatients with refractory mood disorder (Frye *et al.* 2000; Obrocea *et al.* 2002). In the preliminary (Frye *et al.* 2000) and final (Obrocea *et al.* 2002) analyses, gabapentin demonstrated no better treatment response than placebo in a group of patients with highly refractory bipolar (primarily rapid-cycling) disorder.

There seems to be a marked contrast between the pooled results of the uncontrolled observations (generally positive) and the results of the controlled studies (generally negative). Important limitations of the controlled investigations included maximizing lithium response in the single-blind placebo run-in phase, lack of rigorous compliance assessment, and use of a monotherapy study design in a cohort of patients with primarily rapid-cycling, treatment-refractory illness.

Substance-related disorders (off-label). Mood-stabilizing anticonvulsants such as divalproex sodium and carbamazepine may be useful in the treatment of alcohol abuse in bipolar disorder (Malcolm *et al.* 2001). Gabapentin has been shown to reduce excitability and convulsions in animal models of alcohol withdrawal (Watson *et al.* 1997). Its lack of hepatic metabolism, CYP enzyme induction, protein binding, and addictive potential make gabapentin a potentially useful compound in this patient population.

Gabapentin's potential utility in the treatment of alcohol withdrawal was examined after initial positive reports emerged (Bozikas *et al.* 2002). One study demonstrated

that gabapentin had efficacy comparable to that of phenobarbital in treating alcohol withdrawal (Mariani *et al.* 2006), although another controlled trial did not substantiate gabapentin's benefit over placebo (Bonnet *et al.* 2003). In a post hoc analysis (Bonnet *et al.* 2007), there was a significantly greater increase in the Profile of Mood States vigor subscore in the gabapentin group versus the placebo group; this response was particularly robust in patients with comorbid mild depression.

Despite the conflicting findings regarding gabapentin's efficacy in alcohol withdrawal, its therapeutic benefit in the sleep-disturbance component of alcohol withdrawal syndrome is now recognized. In a study in outpatients with DSM-IV-confirmed alcohol dependence who were experiencing persistent insomnia (Karam-Hage and Brower 2003), low-dose gabapentin (mean 900 mg at bedtime) was associated with greater improvement in sleep problems compared with trazodone, as assessed with the Sleep Problems Questionnaire. In another study, gabapentin was associated with significantly greater reductions in self-reported sleep disturbances and daytime sleepiness in outpatients being treated for alcohol withdrawal compared with lorazepam (Malcolm *et al.* 2007).

A 4-week randomized, placebo-controlled, double-blind study evaluated gabapentin utility in the prevention of alcohol use relapse (Furieri and

Nakamura-Palacios 2007). After detoxification, 60 men with DSM-IV-confirmed alcohol dependence who had been consuming on average 17 drinks per day for the preceding 3 months were randomly assigned to gabapentin (300 mg bid) or placebo. The gabapentin group showed significant reductions in number of drinks per day, percentage of heavy drinking days, and craving for alcohol (specifically automaticity of drinking) as well as an increase in percentage of days abstinent. In a study in 150 individuals with DSM-IV-confirmed alcohol dependence, the addition of gabapentin to naltrexone was reported to significantly improve drinking outcomes compared with naltrexone alone or placebo (Anton *et al.* 2011). Another clinical trial examined linear dose effects of gabapentin on alcohol-related insomnia, dysphoria, and craving in patients with DSM-IV-confirmed alcohol dependence (Mason *et al.* 2014). In this 12-week randomized double-blind trial (*n* = 150), evidence of a linear dose response (gabapentin 1,800 mg > gabapentin 900 mg > placebo) was found for abstinence, absence of heavy drinking (defined as [?] 4 and [?] 5 drinks/day for women and men, respectively), mood (i.e., improvement), sleep (i.e., sleep quality), and craving (i.e., reduction).

In a more recent randomized clinical trial in patients with alcoholism, gabapentin was significantly more effective than placebo in decreasing heavy drinking days and heavy alcohol use, with greater pretreatment alcohol withdrawal symptoms predicting a good response (Anton *et al.* 2020). In their meta-analysis of gabapentin, Kranzler *et al.* (2019) also noted statistically significant benefit for gabapentin in deceasing the percentage of heavy alcohol use days.

Finally, in a proof-of-concept randomized controlled study in 50 treatment-seeking outpatients with DSM-IV-confirmed cannabis dependence, gabapentin 1,200 mg/day was significantly more effective than placebo in reducing cannabis use and decreasing withdrawal symptoms (Mason *et al.* 2012).

Side Effects and Toxicology

Gabapentin has a highly favorable side-effect profile that has been remarkably consistent across controlled studies of diverse disease states. Sedation, drowsiness, and dizziness have long been reported. Ataxia, dry mouth, infection, and asthenia have been reported in at least one placebo-controlled study.

Adverse events caused by gabapentin are uncommon but can have serious psychiatric implications. Gabapentin-induced hypomania and mania have been reported (Leweke *et al.* 1999; Short and Cooke 1995). The controlled study in mania did not report data on the percentage of patients experiencing exacerbation of mania secondary to gabapentin treatment (Pande *et al.* 2000a). Gabapentin also has been associated with aggression, both in pediatric epilepsy (Wolf *et al.* 1995) and in adult mania (Pinninti and Mahajan 2001).

Gabapentin has a broad therapeutic index and appears to be safe in overdose. The broadness of the therapeutic index is most likely related to its nonlinear bioavailability secondary to a saturable transport carrier (McLean 1999).

The drug appears to be abusable, as seen in a number of published case series and epidemiological surveys (Evoy *et al.* 2017; Mersfelder and Nichols 2016), with greater rates of misuse seen in substance abuse settings.

Drug-Drug Interactions

Given its lack of hepatic metabolism, absence of CYP autoinduction, and minimal plasma protein binding, gabapentin does not affect levels of anticonvulsant drugs; similarly, gabapentin's pharmacokinetic characteristics do not change when the drug is coadministered with hepatically metabolized anticonvulsants (Pfizer 2017). However, gabapentin's renal excretion does pose a potential risk when the drug is used concomitantly with lithium.

Although the therapeutic index for gabapentin is large, the safety window for lithium is not. In a pharmacokinetic study examining the effect of gabapentin versus placebo on a single 600-mg dose of lithium, there was no difference in maximum lithium concentration, time to reach the maximum lithium concentration, or area under the curve (AUC) in 13 patients receiving steady-state gabapentin (mean dose of 3,645.15 +- 931.5 mg) compared with those receiving steady-state placebo (Frye *et al.* 1998).

It is important to emphasize that this study was conducted in a patient population with normal renal function; cases of reversible renal impairment associated with gabapentin have been reported (Grunze *et al.* 1998).

Summary for Gabapentin

Results of controlled studies of gabapentin clearly suggest its efficacy in several medical conditions, including complex partial epilepsy, postherpetic neuropathy, restless legs syndrome, diabetic neuropathy, and migraine headache. Data also clearly suggest gabapentin's benefit in several off-label psychiatric uses such as substance-related abstinence or craving, mood disorders, and some anxiety disorders. Conclusions regarding gabapentin's efficacy in amyotrophic lateral sclerosis, essential tremor, parkinsonism, social anxiety disorder, or panic disorder are less clear, either because of positive controlled studies with small sample sizes or because of negative studies. Its role as a mood stabilizer is not clearly established. Gabapentin has a favorable pharmacokinetic profile, and its lack of hepatic metabolism is a particular advantage in patients with compromised liver function. Its minimal drug-drug interactions, low risk of toxicity, and benign side-effect profile make gabapentin a useful addition to the pharmacopoeia.

Pregabalin

Pregabalin is an anticonvulsant drug approved by the FDA for the adjunctive treatment of partial-onset seizures in adults. It is also approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. Like many of the newer anticonvulsant agents, pregabalin has been evaluated in carefully controlled studies for possible utility in neurological and psychiatric conditions other than primary epilepsy.

Structure-Activity Relations

Pregabalin [(3S)-3-(aminomethyl)-5-methylhexanoic acid] is a synthetic analog of GABA (Figure 40-2).

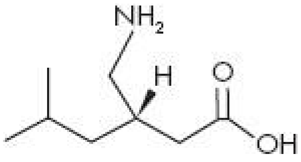

FIGURE 40-2. Chemical structure of pregabalin.

Pharmacological Profile and Mechanism of Action

Pregabalin, like gabapentin, is a structural analog of the inhibitory neurotransmitter GABA. Pregabalin showed greater potency than gabapentin in preclinical models of epilepsy, pain, and anxiety (Hamandi and Sander 2006). Despite being a GABA structural analog, pregabalin has no clinically significant effect at either the $GABA_A$ or the $GABA_B$ receptor and is not converted metabolically into GABA or a GABA agonist (Kavoussi 2006). Furthermore, pregabalin does not bind to any serotonergic, dopaminergic, or glutamatergic receptors. It does bind to the a_2d subunit of the presynaptic voltage-gated calcium channel, modulating the release of excitatory neurotransmitters (Dooley *et al.* 2002; Kavoussi 2006). In contrast with GABA reuptake-inhibitory anticonvulsants (e.g., tiagabine) or anticonvulsants that modulate enzymatic activity related to GABA production (e.g., vigabatrin), pregabalin has no direct GABA reuptake-inhibitory effects or GABA transaminase-inhibiting effects.

Formulations

Pregabalin is available in multiple dosage forms (Pfizer 2018; 2020), including oral capsules (25, 50, 75, 100, 150, 200, 225, and 300 mg), extended-release tablets (82.5, 165, and 330 mg), and an oral solution (100 mg/5 mL). Generic equivalent products are also available.

Pharmacokinetics and Disposition

Pregabalin exhibits linear pharmacokinetics and is not associated with any significant protein binding or hepatic metabolism. Immediate-release pregabalin products have an oral bioavailability that is greater than 90% and independent of dose. With immediate-release pregabalin products, steady-state plasma levels are generally achieved within 24-48 hours, and administration with food has no clinically significant effect on the extent of absorption or on elimination (Pfizer 2018). The elimination half-life of the drug is approximately 6.5 hours (Montgomery 2006). Because pregabalin is highly lipophilic but not bound to plasma proteins, it readily crosses the blood-brain barrier. Pregabalin is primarily (> 90%) excreted renally unchanged, with no active metabolites. Dosage adjustment is required for patients with renal impairment.

Pregabalin does not induce or inhibit CYP enzymes, nor do CYP enzyme inhibitors alter its pharmacokinetics. The bioavailability of pregabalin extended-release tablets is reduced if they are taken on an empty stomach (Pfizer 2020). The AUC is approximately 30% lower when tablets are taken on an empty stomach than when taken after an evening meal. With repeated administration (in which each new dose is taken before elimination of the previous dose), steady state is achieved within approximately 48-72 hours.

Indications and Efficacy

Epilepsy

Several placebo-controlled studies have evaluated pregabalin in the treatment of patients with refractory partial epilepsy (Elger *et al.* 2005; Hamandi and Sander 2006). Response rates for pregabalin dosed at 600 mg/day were similar to those reported in other trials of antiepileptic drugs in refractory epilepsy. The study by Elger *et al.* (2005) showed that pregabalin administered in either fixed or flexible dosages was highly effective and generally well tolerated as an add-on therapy for partial seizures with or without secondary generalization.

Nonepilepsy Neurological Conditions

Four placebo-controlled studies have evaluated the efficacy of pregabalin in neuropathic pain (Dworkin *et al.* 2003; Freynhagen *et al.* 2005; Sabatowski *et al.* 2004; van Seventer *et al.* 2006). The first (Dworkin *et al.* 2003) was an 8-week parallel-group, double-blind, placebo-controlled, randomized multicenter trial, in which patients with postherpetic neuralgia were randomly assigned to either pregabalin 600 mg/day (300 mg/day if they had reduced creatinine clearance) or placebo. At the study endpoint, a significantly greater decrease in mean pain scores was found for patients treated with pregabalin compared with those receiving placebo; this improvement was identified as early as day 2 and was maintained throughout the 8 weeks of double-blind treatment. In the second study (Freynhagen *et al.* 2005), patients with chronic postherpetic neuralgia or diabetic peripheral neuropathy were randomly assigned to placebo, flexible-dosage pregabalin titrated upward to a maximum of 600 mg/day, or fixed-dosage pregabalin at 300 mg/day for the first week followed by 600 mg/day for the remaining 11 weeks. Both flexible-and fixed-dosage pregabalin significantly reduced endpoint mean pain scores and were significantly superior to placebo in improving pain-related sleep interference.

In the third study, van Seventer *et al.* (2006) evaluated pregabalin (150, 300, or 600 mg bid) versus placebo in 370 patients with postherpetic neuralgia. At the endpoint, significantly greater dose-proportional pain relief was evident among patients who received pregabalin versus placebo. Sleep interference in all pregabalin groups was

significantly improved at endpoint. Similar results were obtained in the fourth study (Sabatowski *et al.* 2004), which reported improvement in sleep and mood disturbance in patients treated with pregabalin. In total, these four studies showed benefit in pain reduction, sleep improvement, and mood associated with pregabalin treatment. The most common side effects were dizziness, peripheral edema, weight gain, and somnolence.

Freeman *et al.* (2008) conducted a pooled analysis of data from seven published randomized placebo-controlled trials encompassing 400 patients with diabetic peripheral neuropathy. The primary outcome measure was change from baseline to endpoint in mean pain score from patients' daily pain diaries. With three-times-daily administration, all pregabalin dosages (150, 300, and 600 mg/day) produced significantly greater reductions in pain and pain-related sleep interference compared with placebo. With twice-daily administration, only the 600-mg/day dosage showed efficacy. Pregabalin's pain-reducing and sleep-improving properties appeared to be positively correlated with dosage, with the greatest effect observed in patients treated with 600 mg/day.

Fibromyalgia

Pregabalin was the first medication to receive an FDA indication for the treatment of fibromyalgia. Fibromyalgia is a common chronic pain disorder characterized by widespread diffuse musculoskeletal pain and tenderness frequently accompanied by significant psychiatric comorbidity, including fatigue, sleep disturbance, and mood and anxiety disorders. Classifications of disease severity for fibromyalgia have been published by the American College of Rheumatology (Wolfe *et al.* 1990). The prevalence of fibromyalgia in the U.S. population is estimated at 2%, with higher rates in adult women than in men (Arnold *et al.* 2007).

Three placebo-controlled studies--two focused on acute treatment (Crofford *et al.* 2005; Mease *et al.* 2008) and one on relapse prevention (Crofford *et al.* 2008)--evaluated pregabalin's efficacy in the treatment of patients with fibromyalgia. In the first study, an 8-week double-blind, randomized, placebo-controlled investigation of pregabalin (150, 300, and 450 mg/day) versus placebo, the 450 mg/day dosage was associated with significantly greater reductions in the average severity of pain compared with placebo (Crofford *et al.* 2005). Sleep improvement was noted at both the 300-and 450-mg daily dosages. Dizziness and somnolence were the most frequent adverse events. In recognition of the large overlap of psychiatric comorbidity in fibromyalgia, Arnold *et al.* (2007) conducted a post hoc analysis of the Crofford *et al.* (2005) study to assess symptoms of anxiety and depression and their impact on pregabalin treatment. Of 529 patients who had enrolled in pregabalin treatment for fibromyalgia, significantly more endorsed anxiety symptoms (71%) than depressive symptoms (56%). Improvement in pain symptoms with pregabalin versus placebo did not depend on baseline anxiety or depression; in fact, 75% of the pain reduction was not explained by improvements in mood and/or anxiety.

In the second study, 748 patients with fibromyalgia a 13-week double-blind, placebo-controlled multicenter trial were randomly assigned to either placebo or pregabalin at dosages of 300, 450, or 600 mg/day (dosed twice daily) (Mease *et al.* 2008). The primary outcome measure was symptomatic relief of pain associated with fibromyalgia, as measured by a mean pain score from an 11-point numeric rating scale

(0 = no pain; 10 = worst possible pain) from patients' daily diaries. Patients in all pregabalin groups showed statistically significant improvement in endpoint mean pain scores as well as in sleep.

In the third study, pregabalin was evaluated in nearly 600 patients with fibromyalgia in the Fibromyalgia Relapse Evaluation and Efficacy for Durability of Meaningful Relief trial (Crofford *et al.* 2008). This study included an initial 6-week open-label phase followed by 26 weeks of double-blind treatment with continued pregabalin or blind substitution with placebo. The primary outcome measure was time to loss of therapeutic response, defined as a less than 30% reduction in pain or worsening of symptoms of fibromyalgia. Time to loss of therapeutic response was significantly greater for the pregabalin group than for the placebo group, with Kaplan-Meier estimates of time to event showing that half of the placebo group had relapsed by day 19, whereas half of the pregabalin group had still not lost response by trial end.

Finally, pregabalin was investigated as an adjunct to antidepressant medication in patients with fibromyalgia and comorbid depression (Arnold *et al.* 2015). In this randomized, placebo-controlled, double-blind crossover study, patients receiving stable treatment with selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor antidepressants were randomly assigned to adjunctive pregabalin or placebo for 6 weeks, followed by a 2-week taper/washout phase and a crossover to the opposite adjunctive condition for another 6 weeks. Mean scores on measures of pain, anxiety, depression, and fibromyalgia impact all showed significantly greater improvement with adjunctive pregabalin compared with placebo.

Anxiety Disorders

Generalized anxiety disorder. Findings from four placebo-controlled studies contributed to the approval of pregabalin in Europe for generalized anxiety disorder (Montgomery *et al.* 2006; Pande *et al.* 2003; Pohl *et al.* 2005; Rickels *et al.* 2005). In the first study (Pande *et al.* 2003), 276 patients with generalized anxiety disorder were randomly assigned to pregabalin 150 or 600 mg/day, lorazepam 6 mg/day, or placebo. The 6-week trial included a 1-week placebo lead-in, 4 weeks of blind treatment, and a 1-week taper. The primary efficacy outcome measure was the endpoint Hamilton Anxiety Scale (Ham-A) score. The mean decrease in Ham-A total score from baseline to endpoint in all three active-treatment groups (pregabalin 150 or 600 mg/day and lorazepam 6 mg/day) was significantly greater than the decrease in the placebo group. Percentages of subjects who met a secondary outcome measure--reduction of 50% or greater in Ham-A score--were significantly higher in the pregabalin 600-mg/day group (46%) and the lorazepam group (61%) than in the placebo group (27%). There were no significant differences in response rates by either definition between patients receiving pregabalin 150 mg/day and those receiving placebo.

In the second study, Pohl *et al.* (2005) evaluated twice-daily versus three-times-daily dosing of pregabalin in a 6-week double-blind, placebo-controlled trial. In this study, 250 patients with generalized anxiety disorder were randomly assigned to pregabalin (100 mg bid, 200 mg bid, or 150 mg tid) or placebo. Mean improvement in Ham-A total score was significantly greater with pregabalin at all three dosages than with placebo. Pairwise comparisons of twice-daily versus three-times-daily dosing showed no significant differences in outcome. All three pregabalin groups showed significantly greater improvement compared with placebo at endpoint.

In the third study, which had a 4-week design, Rickels *et al.* (2005) randomly assigned 454 patients with generalized anxiety disorder to receive pregabalin (300, 450, or 600 mg/day), alprazolam (1.5 mg/day), or placebo. The primary outcome measure was change in total Ham-A score from baseline to endpoint. Compared with the placebo group, all treatment groups showed significantly greater reductions in mean Ham-A total score at last-observation-carried-forward analysis. A significantly greater proportion of patients in the pregabalin (all dosages) and alprazolam groups met the endpoint response criterion of a 50% or greater reduction in Ham-A total score than in the placebo group. The response rate for the group receiving pregabalin 300 mg/day (61%) was significantly higher than that for the alprazolam group (43%).

In the only pregabalin study with an active antidepressant comparator to date, Montgomery *et al.* (2006) randomly assigned 421 patients with generalized anxiety disorder to 6 weeks of double-blind treatment with pregabalin (400 or 600 mg/day), venlafaxine (75 mg/day), or placebo. The primary outcome measure was change in Ham-A total score from baseline to last-observation-carried-forward analysis. Pregabalin (both dosages) and venlafaxine produced significantly greater improvement in Ham-A total score than did placebo. Patients receiving pregabalin 400 mg/day experienced significantly greater improvement in all primary and secondary outcome measures compared with those receiving placebo. Rates of discontinuation associated with adverse events were highest in the venlafaxine group (20.4%), followed by the pregabalin 600 mg/day (13.6%), pregabalin 400 mg/day (6.2%), and placebo (9.9%) groups.

Other trials have followed in the wake of these earlier studies. A meta-analysis of seven trials pointed to pregabalin's greater efficacy versus placebo in generalized anxiety disorder, although the effect sizes were relatively small (approximately 0.35 for psychic anxiety symptoms) (Boschen 2011; also see Generoso *et al.* 2017). Pregabalin has also been reported to be an effective adjunctive treatment for patients whose generalized anxiety disorder symptoms are nonresponsive to selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor therapy (Rickels *et al.* 2012). However, a recent add-on study in patients with generalized anxiety disorder or major depressive disorder whose symptoms had not responded to escitalopram failed to show statistically significantly greater benefit with pregabalin compared with placebo (Fountoulakis *et al.* 2019).

Social anxiety disorder. In a study by Pande *et al.* (2004), 135 patients with social anxiety disorder were randomly assigned to 10 weeks of double-blind treatment with a low or high pregabalin dosage (150 vs 600 mg/day) or placebo. The primary outcome measure was change in LSAS total score from baseline to endpoint. Patients randomly assigned to pregabalin 600 mg/day showed significantly greater decreases in LSAS total score compared with those receiving placebo. Significant differences between high-dosage pregabalin and placebo were also noted on several secondary measures, including the LSAS subscales Total Fear, Avoidance, Social Fear, and Social Avoidance. Low-dosage pregabalin (150 mg/day) was not significantly better than placebo. Somnolence and dizziness were the most frequently reported adverse events. In a study in 329 patients with social anxiety disorder, pregabalin 600 mg/day (but not 300 or 450 mg/day) separated from placebo (Feltner *et al.* 2011), a finding consistent with the dosage recommendation of 600 mg/day for efficacy in this disorder. Finally, a long-term study in 153 patients who had responded to an initial course

of pregabalin therapy indicated that 450 mg/day was effective as a maintenance treatment in social anxiety disorder (Greist *et al.* 2011).

Substance-Related Disorders

As noted previously, pregabalin has no hepatic metabolism and is excreted essentially unchanged in the urine. This pharmacokinetic profile is ideal for patients who abuse alcohol or are alcohol dependent and have elevated transaminases but need safe, efficacious treatment for symptoms of alcohol withdrawal. Pregabalin's anticonvulsant, analgesic, and anxiolytic properties and potential utility in alcohol-related disorders were examined in a preclinical study using a mouse model of alcohol dependence (Becker *et al.* 2006). Controlled clinical studies of pregabalin in alcohol-dependent patients are needed.

A study in patients with generalized anxiety disorder indicated that pregabalin was efficacious in facilitating discontinuation of long-term benzodiazepine therapy (Hadley *et al.* 2012).

Side Effects and Toxicology

In general, the side effects commonly occurring with pregabalin treatment have been mild and not associated with a severity sufficient to warrant drug discontinuation. The most frequently reported symptoms have been dizziness, sedation, dry mouth, edema, blurred vision, weight gain, and concentration difficulty. In controlled clinical trials with pregabalin, significant weight gain ([?] 7% over baseline) was observed in 9% of patients treated with pregabalin compared with 2% of patients receiving placebo. Pregabalin treatment does not seem to be associated with significant changes in heart rate, blood pressure, respiration, or electrocardiogram measures. Peripheral edema has occurred in a small percentage of patients, but only in rare circumstances has it been identified as severe.

Pregabalin is a U.S. Drug Enforcement Agency (DEA) schedule V drug. Available preclinical and clinical data suggest that pregabalin has very low abuse liability and is unlikely to produce significant physical dependence. There have been postmarketing reports of angioedema and hypersensitivity in patients treated with pregabalin (Pfizer 2018). As noted earlier for gabapentin, pregabalin has been reported to be subject to abuse, particularly in substance abuse settings and among individuals with opioid dependence (Evoy *et al.* 2017).

Drug-Drug Interactions

Pregabalin does not induce or inhibit CYP enzymes, nor do CYP enzyme inhibitors alter its pharmacokinetics as a consequence. Therefore, hepatic and CYP drug-drug interactions are not relevant when pregabalin is part of a complex polypharmacotherapy regimen. Because of the drug's renal elimination, dosage adjustment is required for patients with renal impairment. To date, no pharmacokinetic drug-drug interactions have been identified. There is some literature to suggest that there can be an additive cognitive impairment when pregabalin is taken in conjunction with oxycodone and that pregabalin may potentiate the effects of lorazepam and alcohol (Pfizer 2018).

Summary for Pregabalin

Controlled studies of pregabalin clearly indicate its efficacy in complex partial epilepsy, postherpetic neuropathy, diabetic neuropathy, fibromyalgia, generalized anxiety disorder, and social anxiety disorder. Like gabapentin, pregabalin has a favorable pharmacokinetic profile, with particular advantages in patients with compromised hepatic function. Its minimal drug-drug interactions, low risk of toxicity, and favorable side-effect profile make pregabalin a useful addition to the pharmacopoeia.

Conclusion

There is increasing interest in the use of gabapentoid drugs in mood and anxiety disorders. Both gabapentin and pregabalin have demonstrated efficacy for pain, fibromyalgia, and specific anxiety disorders. Gabapentin also seems to have potential use in cannabis and alcohol use disorders. To date, the use of gabapentin and pregabalin in the treatment of bipolar disorder has not been demonstrated in controlled clinical trials.

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CHAPTER 41

Lamotrigine

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History and Discovery

During the clinical development of lamotrigine as a treatment for intractable seizures, improved mood in lamotrigine-treated patients was anecdotally reported. Smith *et al.* (1993) found that when lamotrigine was added to an existing antiepileptic drug regimen for 81 patients with epilepsy, they reported significantly higher levels of happiness and perceived internal locus of control. The lack of correlation between perceived happiness and changes in seizure frequency or severity suggested that lamotrigine may affect mood independent of its antiepileptic effect.

Structure-Activity Relations and Pharmacological Profile

Lamotrigine (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine, $C_9H_7Cl_2N_5$) (Figure 41-1) is an antiepileptic drug of the phenyltriazine class that is chemically unrelated to carbamazepine, valproic acid, phenobarbital, phenytoin, and other established antiepileptic drugs. Lamotrigine seemingly does not inhibit the reuptake of monoamines but has weak inhibitory effects at serotonin$_3$ (5-HT$_3$) receptors. Lamotrigine does not have high binding affinity to adrenergic, dopaminergic, GABAergic, histaminergic, kappa opioid, sigma, or muscarinic acetylcholine receptors, but it inhibits use-dependent sodium channels, allowing continued normal depolarizations while suppressing paroxysmal burst firing encountered in seizures and hypoxic insult.

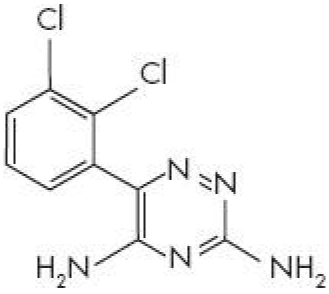

FIGURE 41-1. Chemical structure of lamotrigine.

Pharmacokinetics and Disposition

Oral lamotrigine is rapidly absorbed with negligible first-pass metabolism, and its absorption is not affected by food. Peak plasma concentrations are reached in approximately 1.4-4.8 hours. Lamotrigine's half-life is approximately 25 hours but can be highly variable. For example, in drug-naive adults, the half-life of lamotrigine is 24.1-35 hours (Garnett 1997). In patients receiving other antiepileptic drugs, the half-life can vary from 12.6 to 58 hours (GlaxoSmithKline 2023).Lamotrigine is approximately 55% bound to plasma proteins and is unlikely to significantly interact with drugs that are highly protein bound. Metabolism is primarily achieved by competitive glucuronic acid conjugation. The pharmacokinetics of lamotrigine are linear within a dosage range of 100-700 mg/day (Leach *et al.* 1995). Clearance is reduced in renal insufficiency and hepatic disease.

Estradiol upregulates uridine diphosphate-glucuronosyltransferase UGT1A4 (Chen *et al.* 2009), an enzyme that catalyzes 90% of lamotrigine conjugation (Fotopoulou *et al.* 2009). The rate of lamotrigine clearance increases during each trimester of pregnancy, reaching a peak of 330% of baseline clearance by gestational age 32 weeks (Pennell *et al.* 2004). Active monitoring of lamotrigine levels during pregnancy is recommended in the neurology setting (Harden *et al.* 2009), but the usefulness of monitoring lamotrigine levels during psychiatric treatment during pregnancy remains unclear (Deligiannidis *et al.* 2014). However, if lamotrigine dosing has been increased throughout pregnancy, then the dosage should be decreased immediately after delivery by 20%-25% to prevent toxicity (Clark *et al.* 2013).

Mechanism of Action

Lamotrigine's mechanism of action remains unknown, although its ability to block sodium and N-type calcium channels (Grunze *et al.* 1998) and inhibit glutamate release is believed to be key to its antiepileptic and mood-stabilizing effects. Presynaptic inhibition of voltage-and use-sensitive sodium channels, calcium channels, and potassium channels is believed to result in decreased release of glutamate. Meanwhile, lamotrigine may reduce postsynaptic glutamatergic transmission through suppression of postsynaptic a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (Lee *et al.* 2008). Lamotrigine may also increase brain levels of *N*-acetylaspartate to enhance neuronal viability and prevent cell death from excessive glutamatergic tone (Croarkin *et al.* 2015).

Indications and Efficacy

In 2003, the FDA approved lamotrigine for use in the maintenance treatment of bipolar I disorder. Lamotrigine is also indicated for adjunctive antiepileptic therapy in adults and pediatric patients (age [?] 2 years) with partial seizures, generalized seizures secondary to Lennox-Gastaut syndrome, or primary and generalized tonic-clonic seizures as well as for monotherapy in patients (age [?] 16 years) with partial seizures (GlaxoSmithKline 2023).

Maintenance Therapy in Bipolar I Disorder

Two large randomized, double-blind, placebo-controlled multicenter investigations led to FDA approval of lamotrigine as a maintenance treatment for bipolar I disorder (Bowden *et al.* 2003; Calabrese *et al.* 2003). Both studies used a relapse-prevention design, in which patients with bipolar I disorder were treated with lamotrigine, and their symptoms improved and stabilized before random assignment to lamotrigine, lithium, or placebo (Gao *et al.* 2009, 2016).

One study enrolled patients who were or had recently been in a manic, hypomanic, or mixed state (Bowden *et al.* 2003). Another study enrolled patients who were or had recently been depressed (Calabrese *et al.* 2003). In the initial analysis and a post hoc analysis (Goodwin *et al.* 2004), both lamotrigine and lithium were significantly superior to placebo in delaying the time to intervention for any mood episode regardless of index episodes. Lamotrigine but not lithium was significantly superior to placebo in prolonging the time to a depressive episode; in addition, lithium but not lamotrigine was significantly superior to placebo in prolonging the time to a manic, hypomanic, or mixed episode. However, lithium and lamotrigine had similar effectiveness in preventing any mood, manic or hypomanic, or depressive relapses in a clinical setting (Licht *et al.* 2010). The efficacy of lamotrigine in delaying depressive relapse was also observed in a relapse-prevention study of combination aripiprazole-lamotrigine versus placebo plus lamotrigine (Carlson *et al.* 2012; Gao *et al.* 2016).

Monotherapy or Adjunctive Therapy in Bipolar Depression

Monotherapy in Bipolar Depression

In a previous study, lamotrigine 200 mg/day showed significant antidepressant efficacy in bipolar depression compared with placebo (Calabrese *et al.* 1999). However, the subsequent four randomized placebo-controlled trials failed to show significant differences between lamotrigine monotherapy and placebo (Calabrese *et al.* 2008). In a pooled analysis of

1,072 participants in all five randomized controlled trials, Geddes *et al.* (2009) found that a significantly greater proportion of patients receiving lamotrigine achieved response status compared with placebo. The advantage of lamotrigine over placebo was greater for patients with more severe depression. In another study, a beneficial effect of lamotrigine in bipolar depression was largely limited to depressive cognitions and psychomotor disturbance (Mitchell *et al.* 2013).

The efficacy of lamotrigine in bipolar depression was further demonstrated in a large randomized, double-blind, head-to-head 7-week study examining combination olanzapine-fluoxetine versus lamotrigine (Brown *et al.* 2006). Overall response and remission rates with lamotrigine were comparable to those with olanzapine-fluoxetine. The insignificant difference in response, remission, or relapse between lamotrigine and olanzapine-fluoxetine continued during the 25-week extension, although olanzapine-fluoxetine was superior to lamotrigine in reducing depressive and manic symptoms (Brown *et al.* 2009). The incidence of suicidal and self-injurious behavior was significantly higher among patients receiving lamotrigine compared with those receiving olanzapine-fluoxetine (3.4% vs. 0.5%). The efficacy of lamotrigine for bipolar II depression was also comparable to that of lithium (Suppes *et al.* 2008).

Adjunctive Therapy in Bipolar Disorder

Lamotrigine added to lithium or valproate. Among patients for whom lithium (0.6-1.2 mmol/L) was ineffective for bipolar I or II disorder, lamotrigine added to lithium for at least 2 weeks was significantly more effective in reducing depressive symptoms than placebo added to lithium (van der Loos *et al.* 2009). For nonresponders in both groups, adding paroxetine for another 8 weeks did not change depressive symptoms significantly (van der Loos *et al.* 2010). Responders taking lamotrigine during two phases of treatment had a significantly longer time to relapse or recurrence during the 68-week follow-up period than those receiving placebo (van der Loos *et al.* 2011).

The addition of lamotrigine or quetiapine to lithium or valproate had similar efficacy in acute bipolar depression, but adjunctive therapy was more effective than lithium or valproate monotherapy, with significantly longer survival times (hazard ratio = 6.8) (Gao *et al.* 2020). A temporary increase in depression with monotherapy, even with mild severity for just 1 week, was associated with a significantly increased risk for dropout in the groups in which lamotrigine or quetiapine was not added.

Combination quetiapine-lamotrigine. The combination of quetiapine and lamotrigine was superior to quetiapine alone in reducing depressive symptoms among patients with bipolar I or II depression (Geddes *et al.* 2016). The insignificant difference at 12-week assessment was attributable to an interaction between lamotrigine and folic acid--that is, folic acid reduced the antidepressant efficacy of lamotrigine. However, folic acid alone was not superior to placebo in reducing depressive symptoms, suggesting that folic acid should be avoided when lamotrigine is used as an antidepressant.

Additional Uses

Bipolar Disorder With Rapid Cycling

In several small studies, investigators did not find significant efficacy of lamotrigine over placebo in acute treatment of patients with bipolar disorder with rapid cycling (Kemp *et al.* 2012; Wang *et al.* 2010). In an earlier study, there was no significant difference between lamotrigine and placebo in time to mood relapse in bipolar disorder with rapid cycling (Calabrese *et al.* 2000). However, overall survival time in the study was significantly different between the treatment groups in favor of lamotrigine. For patients with bipolar II disorder, lamotrigine was significantly superior to placebo, with a median survival time of 17 versus 7 weeks.

Bipolar Disorder With Substance Use Disorder

Lamotrigine may be useful in both improving mood and reducing substance use for patients with bipolar disorder and a substance use disorder, although its efficacy in reducing substance use seems to be limited (Brown *et al.* 2003, 2012; Rubio *et al.* 2006). Lamotrigine and valproate may be the preferred agents for comorbid substance use and bipolar disorder (Coles *et al.* 2019).

Children, Adolescents, and Elderly Individuals With Bipolar Disorder

To date, there are no acute randomized placebo-controlled trials of lamotrigine in the treatment of pediatric bipolar disorder. However, open-label studies showed that lamotrigine monotherapy or adjunctive therapy was effective in reducing depressive and manic symptoms in patients with pediatric bipolar disorder (Biederman *et al.* 2010; Chang *et al.* 2006). Open-label and blind data also suggested that lamotrigine monotherapy or adjunctive therapy was efficacious in maintenance treatment of pediatric bipolar disorder (Findling *et al.* 2015; Pavuluri *et al.* 2009). The maintenance efficacy of lamotrigine in 13-to 17-year-olds was more robust than that in 10-to 12-year-olds, suggesting that lamotrigine may be more useful in a subset of older adolescents (Findling *et al.* 2015). Lamotrigine was efficacious and well tolerated in elderly patients with bipolar I or II depression (Sajatovic *et al.* 2011).

Menstrual Cycle-Related Mood Variability in Women With Bipolar Disorder

Because lamotrigine is implicated in the modulation of glutamatergic and potentially GABAergic signaling, this drug has been hypothesized to affect menstrual cycle-related alterations in neurotransmitter activity. Among women with bipolar disorder whose regimens included lamotrigine, less intraindividual variability in mood was evidenced across menstrual cycle phases (Robakis *et al.* 2015). Although the effect was small, it represents preliminary evidence for lamotrigine's potential utility in treating menstrual cycle-entrained mood cyclicity.

Bipolar Mania and Schizophrenia

In early studies in bipolar disorder, lamotrigine failed to separate from placebo in reducing manic symptoms. In two placebo-controlled trials in schizophrenia, lamotrigine used as an adjunct to antipsychotic treatment was not more effective than adjunctive placebo in reducing negative and positive symptoms of schizophrenia (Goff *et al.* 2007); however, in one of the trials, the cognitive composite score improved more with lamotrigine than with placebo. The effect on schizophrenia psychopathology of adding adjunctive lamotrigine to clozapine was not significantly superior to the effect of adding placebo (Zheng *et al.* 2017).

Monotherapy or Adjunctive Therapy for Major Depressive Disorder

Lamotrigine monotherapy for nonrefractory major depressive disorder has not been shown to significantly differ from placebo. In a network meta-analysis, Zhou *et al.* (2015) also did not find significant differences between lamotrigine and placebo adjunctive therapy to antidepressants in major depressive disorder. However, a meta-analysis including all studies of lamotrigine in mood disorders (bipolar depression and major depressive disorder) showed that lamotrigine was significantly superior to placebo in reducing depressive symptoms, but the results in subgroups were less robust (Solmi *et al.* 2016). In a recent meta-analysis including six studies published in Chinese, Goh *et al.* (2019) found that lamotrigine augmentation was effective in reducing depressive symptoms for patients with treatment-resistant major depressive disorder.

Obsessive-Compulsive Disorder and Eating Disorders

Lamotrigine may be used in combination with selective serotonin reuptake inhibitors or monotherapy for OCD (Hirschtritt *et al.* 2017; Zhou *et al.*

2019). However, lamotrigine-induced OCD or obsessive behavior in patients with bipolar disorder has been reported (Kemp *et al.* 2007; Sharma and Doobay 2019). Lamotrigine with dialectical behavior therapy may improve mood symptoms, behavioral dysregulation, and binge-eating behaviors (Trunko *et al.* 2017). However, lamotrigine 236 +- 150 mg/day had efficacy similar to placebo in reducing binge-eating measures, weight, BMI, and other obsessive-compulsive and impulsive symptoms (Guerdjikova *et al.* 2009).

Borderline Personality Disorder

A lack of efficacy for lamotrigine in borderline personality disorder was demonstrated in a large multicenter randomized, double-blind, placebo-controlled trial of 276 patients (Crawford *et al.* 2018). There was no significant difference between lamotrigine ([?] 400 mg/day) and placebo in the treatment of borderline personality disorder after 52 weeks. Costs of direct care were also similar in the two groups. A meta-analysis of two randomized controlled trials with 330 patients also did not demonstrate any significant difference between lamotrigine and placebo for borderline personality disorder (Pahwa *et al.* 2020).

Dosing Recommendations

The recommended dosing schedule for lamotrigine in adults involves initiating therapy with 25 mg/day for the first 14 days and then increasing to 50 mg/day for weeks 3 and 4 of treatment. During week 5 of treatment, lamotrigine can be increased to 100 mg/day, followed by titration to 200 mg/day during weeks 6 and 7. When lamotrigine is used to augment valproate therapy for adult patients, the recommended titration schedule (rate of dosage escalation) is half the rate for individuals not taking valproate (Table 41-1). The dosage escalation rate for lamotrigine used as an adjunct to treatment with an enzyme-inducing antiepileptic drug is double the rate for patients not taking an enzyme-inducing drug (Table 41-2). For patients older than 12 years with epilepsy, the titration schedule should follow the 2023 product labeling for lamotrigine (GlaxoSmithKline 2023; Table 41-3). To date, no published data support improved efficacy for lamotrigine in the treatment of bipolar disorder at dosages greater than 200 mg/day in the absence of an enzyme inducer. In addition, there is no clear association between serum levels of lamotrigine and measures of affective response.

TABLE 41-1. Recommended titration schedule for lamotrigine for patients with bipolar disorder taking valproate

Week	Dosage
Weeks 1 and 2	25 mg every other day
Weeks 3 and 4	25 mg daily
Week 5	50 mg daily
Week 6	100 mg daily
Week 7	100 mg daily

Note. The usual maintenance dosage when lamotrigine is added to valproate is 100 mg/day.
Source. Adapted from GlaxoSmithKline 2023.

TABLE 41-2. Recommended titration schedule for lamotrigine when used as monotherapy and when added to an enzyme-inducing antiepileptic drug regimen[a] (without valproate)

	For patients NOT TAKING an enzyme-inducing antiepileptic drug regimen[a] and not taking valproate	For patients TAKING an enzyme-inducing antiepileptic drug regimen[a] and not taking valproate

[a] Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to increase the apparent clearance of lamotrigine.

[b] Taken in two divided doses.

Source. Adapted from GlaxoSmithKline 2023.

	For patients NOT TAKING an enzyme-inducing antiepileptic drug regimen[a] and not taking valproate	For patients TAKING an enzyme-inducing antiepileptic drug regimen[a] and not taking valproate
Weeks 1 and 2	25 mg/day	50 mg/day
Weeks 3 and 4	50 mg/day	100 mg/day[b]
Week 5	100 mg/day	200 mg/day[b]
Week 6	200 mg/day	300 mg/day[b]
Usual maintenance dosage	200 mg/day	400 mg/day[b]

[a] Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to increase the apparent clearance of lamotrigine.

[b] Taken in two divided doses.

Source. Adapted from GlaxoSmithKline 2023.

TABLE 41-3. Escalation regimen for lamotrigine in patients older than 12 years with epilepsy

	For patients TAKING valproate[a]	For patients NOT TAKING carbamazepine, phenytoin, phenobarbital, primidone,[b] or valproate[a]	For patients TAKING carbamazepine, phenytoin, phenobarbital, or primidone[b] and NOT TAKING valproate[a]

[a] Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine.

[b] Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified antiepileptic drugs, include estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used with antiepileptic drugs that induce glucuronidation and increase clearance.

Source. Adapted from GlaxoSmithKline 2023.

	For patients TAKING valproate[a]	For patients NOT TAKING carbamazepine, phenytoin, phenobarbital, primidone,[b] or valproate[a]	For patients TAKING carbamazepine, phenytoin, phenobarbital, or primidone[b] and NOT TAKING valproate[a]
Weeks 1 and 2	25 mg every other day	25 mg/day	50 mg/day
Weeks 3 and 4	25 mg every day	50 mg/day	100 mg/day (in two divided doses)
Week 5 onward to maintenance	Increase by 25-50 mg/day every 1-2 weeks	Increase by 50 mg/day every 1-2 weeks	Increase by 100 mg/day every 1-2 weeks
Usual maintenance dosage	With valproate alone: 100-200 mg/day With valproate combined with other drugs that induce glucuronidation: 100-400 mg/day (in one dose or in two divided doses)	225-375 mg/day (in two divided doses)	300-500 mg/day (in two divided doses)

[a] Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine.

[b] Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified antiepileptic drugs, include estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used with antiepileptic drugs that induce glucuronidation and increase clearance.

Source. Adapted from GlaxoSmithKline 2023.

Side Effects and Toxicity

In controlled monotherapy trials of lamotrigine in mood disorders, the drug was associated with headache, nausea, dizziness, and changes in sleep habits (Bowden *et al.* 2004). In randomized trials of lamotrigine in mood disorders, the prevalence of rash did not exceed that of placebo; however, rash is generally recognized as the side effect most likely to significantly complicate clinical use of the drug.

Skin Reactions

The most common lamotrigine-associated rash is an exanthematic maculopapular or morbilliform eruption that is benign. However, a clinically similar eruption may be associated with rarer and more serious systemic hypersensitivity reactions (Guberman *et al.* 1999). Figure 41-2 presents a decision-making algorithm for the management of benign and serious rashes (Calabrese *et al.* 2002). A serious lamotrigine rash is usually confluent with prominent facial and neck involvement. The rash may be tender or have a purpuric or hemorrhagic appearance, or it may be accompanied or preceded by fever, malaise, pharyngitis, anorexia, or lymphadenopathy (Guberman *et al.* 1999). Thus, all patients who develop a rash during the first few months of lamotrigine therapy should be instructed to hold the next dose and immediately seek medical consultation. The greatest risk of rash appears to be during the first 8 weeks of treatment. Nearly all cases of life-threatening rashes caused by lamotrigine have occurred within 2-8 weeks of treatment initiation (GlaxoSmithKline 2023). A rash during the first 5 days of therapy is usually attributable to a nondrug cause. Because immune tolerance to lamotrigine is lost after dosage interruption for more than 1 week, patients should be instructed to resume lamotrigine at the prior initial starting dose and to gradually titrate upward whenever therapy has been interrupted for more than 2 days.

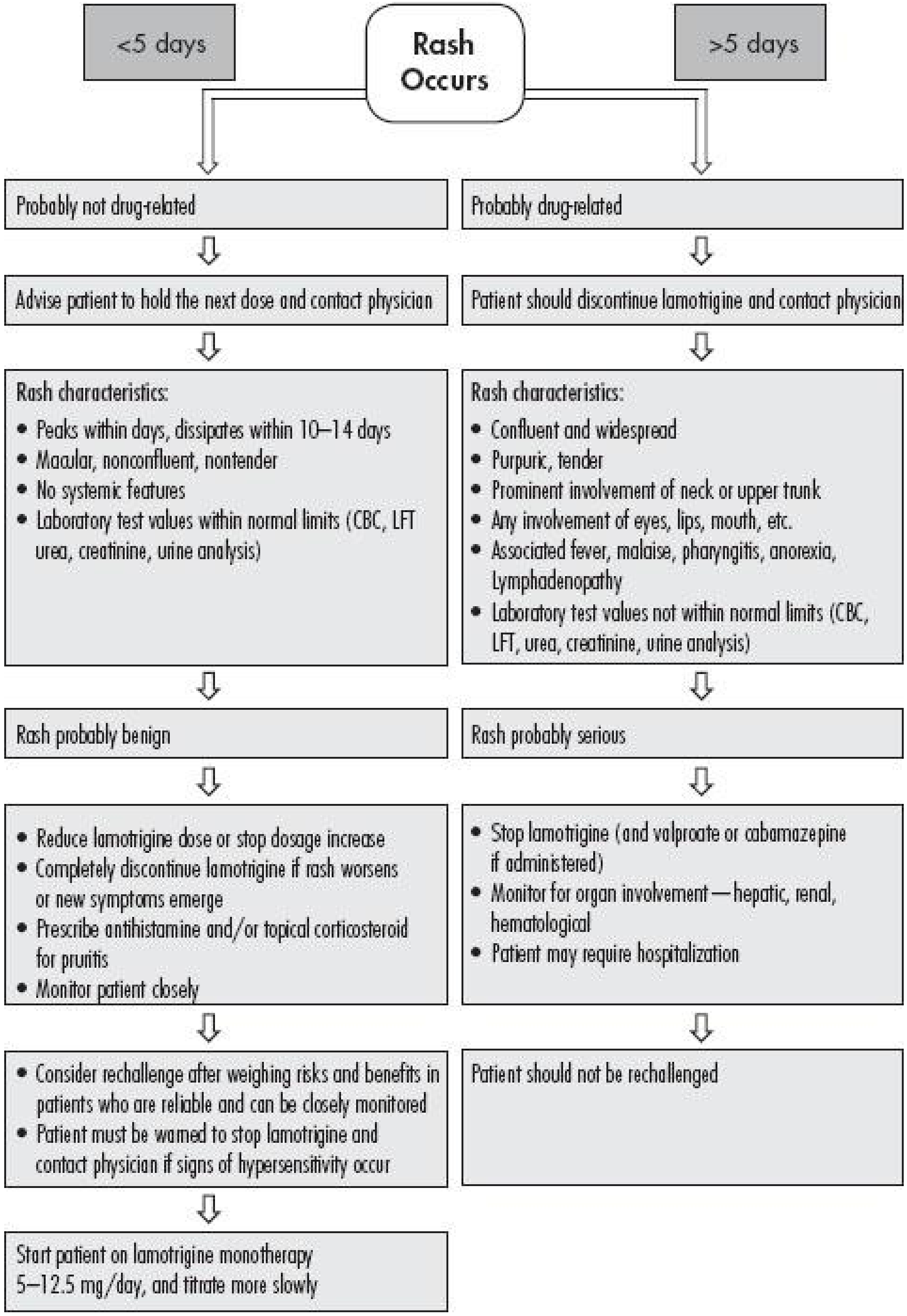
<5 days
Rash Occurs
>5 days
Probably not drug-related
Probably drug-related
Advise patient to hold the next dose and contact physician
Patient should discontinue lamotrigine and contact physician
Rash characteristics:
• Peaks within days, dissipates within 10–14 days
• Macular, nonconfluent, nontender
• No systemic features
• Laboratory test values within normal limits (CBC, LFT urea, creatinine, urine analysis)
Rash characteristics:
• Confluent and widespread
• Purpuric, tender
• Prominent involvement of neck or upper trunk
• Any involvement of eyes, lips, mouth, etc.
• Associated fever, malaise, pharyngitis, anorexia, Lymphadenopathy
• Laboratory test values not within normal limits (CBC, LFT, urea, creatinine, urine analysis)
Rash probably benign
Rash probably serious
• Reduce lamotrigine dose or stop dosage increase
• Completely discontinue lamotrigine if rash worsens or new symptoms emerge
• Prescribe antihistamine and/or topical corticosteroid for pruritis
• Monitor patient closely
• Stop lamotrigine (and valproate or cabamazepine if administered)
• Monitor for organ involvement—hepatic, renal, hematological
• Patient may require hospitalization
• Consider rechallenge after weighing risks and benefits in patients who are reliable and can be closely monitored
• Patient must be warned to stop lamotrigine and contact physician if signs of hypersensitivity occur
Patient should not be rechallenged
Start patient on lamotrigine monotherapy 5–12.5 mg/day, and titrate more slowly

FIGURE 41-2. Clinical management of rash related to lamotrigine treatment.

Note. CBC = complete blood count; LFT = liver function test.

Source. Reprinted from Calabrese JR, Sullivan JR, Bowden CL, et al.: "Rash in Multicenter Trials of Lamotrigine in Mood Disorders: Clinical Relevance and Management." *Journal of Clinical*

Psychiatry 63:1012-1019, 2002. Copyright 2002, Physicians Postgraduate Press. Used with permission.

In early epilepsy trials, rash led to hospitalization and treatment discontinuation or was diagnosed as Stevens-Johnson syndrome (SJS) in 0.3% of adults taking lamotrigine (Calabrese *et al.* 2002). The annual incidence of serious drug-based skin reactions associated with lamotrigine (e.g., SJS, toxic epidermal necrosis [TEN], and drug rash with eosinophilia and systemic symptoms) was highest in 1993 (4.2%) but steadily declined and had stabilized by 1998 (0.02%). A higher starting dose was significantly associated with an increased risk for severe rash, including TEN and SJS (Wong *et al.* 1999). TEN covering 30% or more of the body surface area was recognized as being serious

and life-threatening. In contrast, SJS rashes covering only 10% or less of the body surface area were considered less serious. However, both TEN and SJS are life-threatening and believed to be caused by impaired clearance of toxic drug metabolites that leads to rash, fever, and skin and mucosal slough.

Since 2013, the starting dosage and the titration rate have been widely recognized as two factors contributing to risk of lamotrigine-induced rash. The risk of rash is heightened by exceeding the recommended initial dosage or the rate of dosage escalation of lamotrigine and by coadministering lamotrigine with valproic acid. The risk is also greater in children younger than age 12 years. To minimize the risk of (life-threatening) rash, lamotrigine should be prescribed as described in Tables 41-1 through 41-3. Clinicians should not deviate from the recommended guidance.

Aseptic Meningitis and Hemophagocytic Lymphohistiocytosis

Rare cases of aseptic meningitis in association with lamotrigine have occurred (Boot 2009; Kilfoyle *et al.* 2005; Lam *et al.* 2010). Clinical manifestations include meningismus, photophobia, headache, vomiting, and fever, which can appear as soon as 1 day or as late as 1.5 months after treatment initiation. In some cases, sudden and severe symptoms of meningitis have occurred within minutes of reintroducing lamotrigine. Most patients recover completely once lamotrigine is discontinued (Moris and Garcia-Monco 1999).

Hemophagocytic lymphohistiocytosis, an immune-related and life-threatening event, has occurred with lamotrigine dosages of 25 mg qod to 250 mg/day (Kim *et al.* 2019). Persistent fever, enlarged liver and lymph nodes, skin rash, yellow skin or eyes, easy bleeding, seizure, unsteady gait, and visual changes can occur. Hemophagocytic lymphohistiocytosis can lead to severe blood cell problems and organ failure. Early recognition and treatment are essential to improve outcomes.

Class IB Antiarrhythmic Activity

The blocking effect of lamotrigine on sodium channels has raised concern regarding its impact on ventricular conduction (Harmer *et al.* 2011). Studies with healthy subjects (Dixon *et al.* 2008) and elderly patients with epilepsy (Saetre *et al.* 2009) did not show a significant effect of lamotrigine on cardiac activity. However, in vitro findings showing lamotrigine's effect on cardiac activity from GlaxoSmithKline (2023), the manufacturer of branded lamotrigine (Lamictal), propelled the FDA to add a cardiac safety warning to the drug label. Patients who have second-or third-degree heart block, ventricular arrhythmia, cardiac disease (e.g., myocardial ischemia, heart failure, structural heart disease, Brugada syndrome), or other sodium channel abnormalities should avoid lamotrigine. Concomitant use of lamotrigine with other sodium channel blockers may increase the risk of arrhythmia.

Weight and Metabolic Neutral Effects

Compared with other agents used to treat bipolar disorder, lamotrigine has a neutral weight and metabolic profile (Brown *et al.* 2009; Sachs *et al.* 2006). A post hoc analysis demonstrated that nonobese individuals taking lamotrigine were unlikely to experience a change in weight. However, obese patients were significantly more likely to lose weight with lamotrigine and to gain weight with lithium (Bowden *et al.* 2006).

Safety in Overdose

In a systematic review of 543 cases of lamotrigine toxicity in overdose, which included data from an earlier case series (Lofton and Klein-Schwartz 2004) of 493 single-substance exposures to lamotrigine, Alabi *et al.* (2016) found that the ingested doses of lamotrigine ranged from 100 mg to 40,000 mg. Although the majority of patients (52.1%) experienced no toxic clinical effects, those who developed symptoms reported effects including drowsiness, vomiting, nausea, ataxia, dizziness, and tachycardia. Rare cases of coma, seizures, heart conduction delay, and respiratory depression have been reported (Alabi *et al.* 2016). Two deaths occurred after ingestion of lamotrigine doses of 4,000 mg and 7,500 mg (Alabi *et al.* 2016).

Use During Pregnancy and Lactation

With regard to teratogenic effects, lamotrigine has been assigned an FDA Pregnancy Category C. At conventional dosages, patients taking lamotrigine may have absolute risks for major congenital malformations similar to those of the general population (Andrade 2018; Veroniki *et al.* 2017a). A prospective observational study from 1999 to 2004 reported that children exposed to lamotrigine in utero had higher IQ scores compared with those exposed to valproate, carbamazepine, or phenytoin (Meador *et al.* 2009). However, a significantly increased risk for autism associated with exposure to lamotrigine monotherapy or lamotrigine-valproate was reported (Veroniki *et al.* 2017b).

Lamotrigine may provide protective effects against mood disorder relapse in pregnancy and seems to be a better choice with less risk of teratogenic effects than other anticonvulsant mood stabilizers and lithium, although its long-term effects on development remain uncertain. If lamotrigine is indicated during pregnancy, a minimum effective dose should be used (especially during the first trimester), even though no dose-dependent effect has been observed with lamotrigine for major congenital malformations and IQ (Andrade 2018). In newborns of mothers receiving lamotrigine, umbilical cord concentrations approached those of maternal serum (Ohman *et al.* 2000). Nursing infants demonstrate plasma lamotrigine concentrations that are approximately 23%-50% of maternal levels.

Drug-Drug Interactions

Lamotrigine is not known to inhibit activity of the cytochrome P450 enzyme CYP2D6. However, the addition of adjunctive lamotrigine to enzyme inducers such as carbamazepine, phenytoin, primidone, and phenobarbital decreases lamotrigine plasma concentrations by approximately 40%-50% (Hahn *et al.* 2004). The inducing effect of oxcarbazepine is approximately half that of carbamazepine (Weintraub *et al.* 2005). Because lamotrigine is nearly exclusively metabolized by glucuronidation, the introduction of adjunctive valproate (an enzyme inhibitor) results in immediate and successful competition for metabolism, with resultant increases in half-life.

Oral contraceptives containing estrogen have the potential to decrease serum concentrations of lamotrigine by up to 64% (Sabers *et al.* 2001, 2003). Use of ethinyl estradiol-containing compounds during long-term lamotrigine treatment may require an increase in lamotrigine to as much as twice the recommended target maintenance dose. Conversely, stopping estrogen-containing oral contraceptives, including during the "pill-free" week, may increase lamotrigine levels to a clinically significant range. Progestins, however, are not associated with a decrease in lamotrigine levels (Reimers *et al.* 2005). Patients with HIV receiving combination ritonavir-atazanavir may require a lamotrigine dosage increase of approximately 50% to maintain unchanged lamotrigine serum concentrations (Birbeck *et al.* 2012).

Lamotrigine Recommendations in Treatment Guidelines

Because of the modest effect sizes of lamotrigine as monotherapy in acute treatment of bipolar depression, recommendations for its use in bipolar disorder vary among national and international treatment guidelines. However, the International Society for Bipolar Disorders has consistently designated lamotrigine as a first-line medication for acute treatment of bipolar depression and for maintenance treatment of bipolar disorders (Yatham *et al.* 2013, 2018). This recommendation is based on lamotrigine's comparable efficacy to other FDA-approved agents such as the olanzapine-fluoxetine combination and quetiapine, as well as on lamotrigine's short-term and long-term benign side-effect profiles.

Conclusion

Although lamotrigine was ineffective in the acute treatment of mania, this drug has demonstrated efficacy and effectiveness in reducing depressive symptoms and preventing mood relapse in bipolar disorder similar to those demonstrated by lithium and some antipsychotics. Lamotrigine's neutral effects on body weight and metabolic function and favorable side-effect profile make it an appealing choice for patients who have comorbid metabolic syndrome or who are unable to tolerate other treatments. At present, lamotrigine remains the only antiepileptic drug mood stabilizer with more established efficacy in the depressed illness phase than in mania or hypomania.

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CHAPTER 42

Topiramate

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History and Discovery

The FDA approved topiramate for the treatment of epilepsy in 1996, for migraine prevention in 2004, and in combination with phentermine for chronic weight management in 2012. Reports appearing in the late 1990s of the drug having potential beneficial effects in bipolar disorder led Johnson & Johnson Pharmaceutical Research and Development, the discoverer and manufacturer of topiramate, to conduct a large clinical study program of topiramate in the treatment of acute bipolar mania (McElroy and Keck 2004). Controlled trials of the drug in adult patients with manic or mixed symptoms of bipolar disorder failed to demonstrate significant separation between the topiramate-and placebo-treated groups (Kushner *et al.* 2006; Roy Chengappa *et al.* 2006). However, topiramate has been shown in placebo-controlled trials to be efficacious in the treatment of migraine headache and several neuropsychiatric conditions often comorbid with bipolar disorder, including binge-eating disorder, bulimia nervosa, alcohol use disorder, borderline personality disorder, and psychotropic medication-associated weight gain. In addition, mounting evidence suggests that topiramate augmentation of antipsychotic therapy may reduce psychological symptoms in schizophrenia spectrum disorders.

Structure-Activity Relations and Pharmacological Profile

Topiramate (Figure 42-1) has multiple pharmacological properties that may contribute to its anticonvulsant and neuropsychiatric effects (Langtry *et al.* 1997; Rho and Sankar 1999; Rosenfeld *et al.* 1997; Shank *et al.* 2000; White 2002, 2005; White *et al.* 2007). First, topiramate inhibits voltage-gated sodium channels in a voltage-sensitive, use-dependent manner and thus suppresses action potentials associated with sustained repetitive cell firing (Kawasaki *et al.* 1998; Shank *et al.* 2000). Second, topiramate increases brain GABA levels, possibly by activating a site on the $GABA_A$ receptor, thereby enhancing the inhibitory chloride ion influx mediated by the $GABA_A$ receptor and potentiating GABA-evoked currents (Kuzniecky *et al.* 1998; Petroff *et al.* 2001; Simeone *et al.* 2006). Because this action is not blocked by the benzodiazepine antagonist flumazenil, it is thought that topiramate exerts this effect via an interaction with the $GABA_A$ receptor that is not modulated by benzodiazepines (White *et al.* 2000).

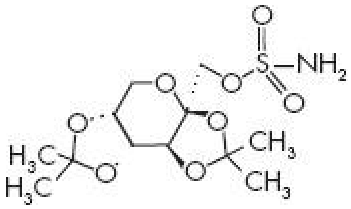

FIGURE 42-1. Chemical structure of topiramate.

Third, topiramate antagonizes glutamate receptors of the a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate subtype and may selectively inhibit glutamate receptor 5 kainate receptors (Kaminski *et* al. 2004). Topiramate has essentially no effect on glutamate *N*-methyl-D-aspartate receptors. AMPA/kainate receptors mediate fast excitatory postsynaptic potentials responsible for excitatory neurotransmission; blockade of kainate-evoked currents decreases neuronal excitability.

Fourth, topiramate negatively modulates high-voltage-activated calcium channels (Zhang *et al.* 2000). Of note, Shank *et al.* (2000) proposed that topiramate's combined effects on voltage-activated sodium channels, $GABA_A$ receptors, AMPA/kainate receptors, and high-voltage-activated calcium channels are unique compared with those of other antiepileptic drugs. Indeed, Schiffer *et al.* (2001) found that pretreatment with topiramate inhibited nicotine-induced increases in mesolimbic extracellular dopamine and norepinephrine, but not serotonin. These authors hypothesized that this property was a result of the drug's ability to affect both GABAergic and glutamatergic function.

Fifth, topiramate weakly inhibits certain carbonic anhydrase isoenzymes, including subtypes II and VI. Carbonic anhydrase is essential for the generation of $GABA_A$-mediated depolarizing responses. By inhibiting carbonic anhydrase, topiramate has been shown to reversibly reduce the $GABA_A$-mediated depolarizing responses evoked by either synaptic stimulation or pressure application of GABA (but not to modify $GABA_A$-mediated hyperpolarizing postsynaptic potentials) (Herrero *et al.* 2002).

Finally, topiramate has several other properties. These include an interaction with glycine receptor channels (Mohammadi *et al.* 2005), effects on mitochondrial permeability (Kudin *et al.* 2004), and antikindling properties in some animal models (Wauquier and Zhou 1996).

Formulations

Topiramate is marketed in capsule ("sprinkle capsule"), tablet, extended-release capsule (Janssen Pharmaceuticals 2012), and oral solution (Azurity Pharmaceuticals 2023) formulations. Topiramate's sprinkle capsule formulation is available in the lowest strengths (15 and 25 mg), and may either be swallowed whole or be opened and sprinkled on soft food. It should be noted that the sprinkle capsule and tablet dosage forms are bioequivalent, whereas the tablet is about 80% bioavailable compared with the oral solution. For patients, the Medication Guides issued with many prescribed drugs provide information on the available dosage forms, strengths, and markings (U.S. Food and Drug Administration 2023). These handouts are valuable for educating patients about proper use of drugs and potential side effects and can help reduce the risk of medication errors and severe adverse effects.

Pharmacokinetics and Disposition

Topiramate has a favorable pharmacokinetic profile (Bialer *et al.* 2004; Doose and Streeter 2002; Langtry *et al.* 1997; Rosenfeld 1997; Shank *et al.* 2000). It is rapidly and almost completely absorbed after oral administration, with bioavailability estimated to be approximately 80%. Peak plasma concentrations are reached within 2-4 hours. Plasma concentration increases in proportion to dose over the pharmacologically relevant dose range. Topiramate is minimally protein bound (9%-17%).

Topiramate is minimally metabolized by the liver in the absence of hepatic enzyme-inducing drugs. This agent inhibits cytochrome P450 enzyme (CYP) 2C19 but not other hepatic CYP enzymes. Topiramate is excreted mostly unchanged (approximately 70%) in the urine. The nonrenal (hepatic) clearance of topiramate increases two-to threefold when the drug is administered with hepatic enzyme-inducing drugs such as carbamazepine and phenytoin. Six minor metabolites have been identified (Shank *et al.* 2000).

Topiramate's elimination half-life is 19-25 hours, and steady state is achieved in about 4 days. The pharmacokinetics of topiramate are linear at the dosage range of 100-1,200 mg/day. The pharmacokinetics of topiramate in children are similar to those in adults, except that clearance is 50% higher, resulting in 33% lower plasma concentrations. Moderate or severe renal failure is associated with reduced renal clearance and increased elimination half-life of topiramate. Moderate or severe liver impairment is associated with clinically insignificant increased plasma concentrations of the drug.

Mechanism of Action

Although the mechanism of topiramate's anticonvulsant action is unknown, it has been hypothesized to be attributable to some combination of the drug's multiple pharmacological properties (Rho and Sankar 1999; Shank *et al.* 2000; White 2002, 2005; White *et al.* 2007). For example, topiramate's anticonvulsant profile, as well as its benefits in treating

substance use and eating disorders, has been hypothesized to be attributable to its dual actions on the GABAergic and glutamatergic systems (Johnson *et al.* 2003, 2005; McElroy *et al.* 2003, 2007; Rho and Sankar 1999; Schiffer *et al.* 2001).

Indications and Efficacy

FDA-Approved Indications

Topiramate is FDA approved for the following indications: as initial monotherapy for patients age 10 years or older with partial-onset or primary generalized tonic-clonic seizures; as adjunctive therapy for adults and pediatric patients ages 2-16 years with partial-onset seizures or primary generalized tonic-clonic seizures; and for patients ages 2 years and older with seizures associated with Lennox-Gastaut syndrome (van Passel *et al.* 2006). Topiramate is also approved for the prophylaxis of migraine headache in adults (Brandes 2005; Bussone *et al.* 2006). In 2012, the FDA approved extended-release topiramate in combination with phentermine (marketed under the trade name Qsymia [Vivus 2023]) for long-term weight management as an adjunct to lifestyle modification for people with obesity or overweight (BMI [?] 30 or [?] 27, respectively; calculated as weight in kilograms divided by height in meters squared) who also have at least one weight-related comorbidity (e.g., hypertension or type 2 diabetes mellitus) (Alfaris *et al.* 2015).

Other Indications

Topiramate is not FDA approved for use in the treatment of any psychiatric disorder. Because the drug was widely used off-label in the treatment of bipolar disorder after it came to market (discussed in the next subsection), Johnson & Johnson Pharmaceutical Research and Development conducted a large study program of topiramate in adults with acute bipolar mania. These placebo-controlled studies failed to demonstrate significant benefit of topiramate over placebo on Young Mania Rating Scale (YMRS) scores (Kushner *et al.* 2006; McElroy and Keck 2004). By contrast, findings from randomized placebo-controlled trials suggest that topiramate may be efficacious in major depressive disorder, schizophrenia, binge-eating disorder, bulimia nervosa, alcohol use disorder, other substance use disorders, and psychotropic-induced weight gain. In addition, growing evidence suggests that topiramate may be helpful in movement disorders, including essential tremor (Ferreira *et al.* 2019) and tic disorders (Billnitzer and Jankovic 2020).

Bipolar Disorder

Five randomized placebo-controlled studies have shown that topiramate monotherapy is not efficacious in the short-term treatment of acute manic or mixed episodes in adults with bipolar I disorder (Kushner *et al.* 2006; McElroy and Keck 2004). All five studies used week 3 as the primary endpoint; in addition, three studies had a week 12 secondary endpoint, two studies had lithium comparator groups, and all trials measured weight as a secondary outcome. In each trial, the primary efficacy outcome--the change in YMRS score from baseline to week 3--failed to show a statistically significant separation between topiramate and placebo. There was also no drug-versus-placebo separation in the three trials with week 12 data. By contrast, in the two trials in which lithium was used, lithium did show statistical superiority to placebo.

Similarly, in the only placebo-controlled study of adjunctive topiramate in bipolar disorder to date, 287 outpatients experiencing a manic or mixed episode according to DSM-IV criteria (American Psychiatric Association 1994) and having a baseline YMRS score of 18 or greater while taking therapeutic levels of valproate or lithium showed similar reductions (40%) from baseline YMRS scores for both topiramate and placebo after 12 weeks (Roy Chengappa *et al.* 2006). In the only placebo-controlled study of topiramate in pediatric bipolar I disorder to date, 56 children and adolescents (ages 6-17 years) experiencing a manic or mixed episode were randomly assigned to topiramate monotherapy or placebo for 4 weeks (Delbello *et al.* 2005). The study was initially designed to enroll approximately 230 participants but was prematurely discontinued when results from the adult mania trials were negative. The decrease in mean YMRS score from baseline to final visit using last-observation-carried-forward analysis was not statistically different between treatment groups. However, a post hoc repeated-measures linear regression model of the primary efficacy analysis showed a statistically significant difference in the slopes of the linear mean profiles ($P = 0.003$).

To date, no placebo-controlled study of topiramate has been conducted with patients with acute bipolar depression. Results from an 8-week single-blind comparison trial in which 36 outpatient adults with bipolar depression were randomly assigned to either topiramate (mean dosage [range] = 176 [50-300] mg/day) or sustained-release bupropion (mean dosage = 250 [100-400] mg/day) suggested that topiramate might have antidepressant properties in some patients with bipolar disorder (McIntyre *et al.* 2002). The percentage of patients whose symptoms met a priori response criteria ([?] 50% decrease from baseline in mean total score on the 17-item Hamilton Rating Scale for Depression) was significant for both topiramate (56%) and sustained-release bupropion (59%).

Depressive Disorders

Two randomized placebo-controlled studies of topiramate in patients with major depressive disorder have been conducted. In the first study, 64 female individuals with DSM-IV recurrent major depressive disorder were randomly assigned to topiramate or placebo for 10 weeks (C. Nickel *et al.* 2005a). Topiramate was superior to placebo in reducing depressive and anger symptoms. All subjects tolerated topiramate well, and there were no suicidal events. In the second study, 53 patients with DSM-IV major depressive disorder that was inadequately responsive to an 8-week trial of a selective serotonin reuptake inhibitor (SSRI) were randomly assigned to adjunctive topiramate (100-200 mg/day) or placebo for 8 weeks (Mowla and Kardeh 2011). Topiramate recipients had a 32% mean decrease in Hamilton Rating Scale for Depression scores, whereas placebo recipients had a mean decrease of 5.5%. Topiramate augmentation also produced significantly greater global improvement in depressive symptoms compared with placebo augmentation. Six patients discontinued topiramate because of side effects, which included loss of appetite, gastric disturbance, memory problems, and akathisia. No suicidal events were reported.

Psychotic Disorders

Studies. Seven randomized placebo-controlled studies of topiramate targeting psychopathology in patients with psychotic disorders have been conducted, with mixed

results. Six of these studies involved patients with schizophrenia. The other involved patients with schizoaffective disorder, bipolar type.

Schizophrenia. In the first schizophrenia study, 26 patients with treatment-resistant illness had topiramate (gradually increased to 300 mg/day) or placebo added to their ongoing antipsychotic regimens over two 12-week crossover treatment periods (Tiihonen *et al.* 2005). In the intent-to-treat analysis, topiramate was superior to placebo in reducing general psychopathological symptoms as assessed with the Positive and Negative Syndrome Scale (PANSS), but no significant improvement in positive or negative symptoms was observed.

In the second study, 66 inpatients with schizophrenia who were being treated with risperidone were randomly assigned to augmentation with topiramate (100 or 200 mg/day) or placebo for 12 weeks (Ko *et al.* 2005). Both dosages of topiramate were superior to placebo in reducing psychopathology, as assessed with the Clinical Global Impression Scale Severity of Illness subscale and the Brief Psychiatric Rating Scale.

In the third study, either topiramate ([?] 300 mg/day) or placebo was added to the clozapine regimens of 32 patients with schizophrenia for 56 days (Afshar *et al.* 2009). At day 56, PANSS total scores and scores for all three subscales (negative symptoms, positive symptoms, and general psychopathology) were significantly improved in the topiramate augmentation group compared with the placebo augmentation group.

In the fourth study, 72 drug-naive patients with schizophrenia were randomly assigned to olanzapine plus topiramate 100 mg/day or olanzapine plus placebo for 12 weeks (Narula *et al.* 2010). Compared with the placebo-treated group, the topiramate-treated group showed significantly greater improvement in PANSS total scores ($P = 0.001$) and general psychopathology measures ($P < 0.001$).

In the fifth study, 43 individuals with treatment-resistant schizophrenia who were receiving clozapine were given adjunctive topiramate ([?] 200 mg/day) or placebo for 24 weeks (Muscatello *et al.* 2011). The addition of topiramate was associated with a significant reduction in bizarre behavior as assessed on the Scale for the Assessment of Positive Symptoms ($P < 0.002$); however, no significant improvement in positive, negative, affective, or overall clinical symptomatology was otherwise seen with topiramate.

In the sixth study, either topiramate (200-300 mg/day) or placebo was added to clozapine for 80 hospitalized patients with schizophrenia for 17 weeks (Behdani *et al.* 2011). At endpoint, add-on topiramate was not superior to add-on placebo in reducing positive, negative, or general psychopathological symptoms as assessed by the PANSS.

Schizoaffective disorder. In the schizoaffective disorder study, 48 patients with a diagnosis of DSM-IV schizoaffective disorder, bipolar type, were randomly assigned (2:1, favoring topiramate) to 8 weeks of double-blind adjunctive treatment with topiramate (100-400 mg/day) or placebo

(Roy Chengappa *et al.* 2007). Patients who had achieved at least a 20% decrease from baseline in their PANSS total scores were given the opportunity to continue for an additional 8 weeks of double-blind treatment. Adjunctive topiramate (nearly 275 mg/day) did not show increased efficacy relative to placebo on the PANSS (the primary outcome measure) or on any of the secondary outcome measures.

Meta-analyses Three meta-analyses have included the seven studies just described, and all concluded that topiramate augmentation of antipsychotics may reduce a range of schizophrenia symptoms. In the first meta-analysis, the authors concluded that topiramate as an adjunct to antipsychotics was effective for symptomatic improvement in patients with schizophrenia spectrum disorders (Zheng *et al.* 2016). The authors of the second meta-analysis concluded that topiramate significantly reduced total, positive, negative, and general psychopathology with minimal side effects in patients with schizophrenia spectrum disorder (Correll *et al.* 2016). In the third meta-analysis, the authors concluded that topiramate reduced overall, positive, and negative symptoms (Okuyama *et al.* 2016).

Case reports. There are several case reports of the successful use of topiramate to treat catatonia in patients with chronic psychotic disorders (McDaniel *et al.* 2006). By contrast, there are also reports of the emergence of psychotic symptoms with topiramate treatment (Duan *et al.* 2019; Duggal and Singh 2004; Miller *et al.* 2010).

Eating and Feeding Disorders.

Five randomized placebo-controlled studies involving individuals with bulimia nervosa (two studies) or binge-eating disorder (three studies) demonstrated that topiramate reduces binge eating in both conditions. An additional randomized placebo-controlled trial reported that phentermine-topiramate reduced binge eating in binge-eating disorder and bulimia nervosa (Safer *et al.* 2020). Yet another randomized controlled trial showed that topiramate reduced nocturnal eating in sleep-related eating disorder.

Bulimia nervosa.

The first bulimia nervosa study was a 10-week trial with 69 subjects. Topiramate (median dosage [range] = 100 [25-400] mg/day) was superior to placebo in reducing the frequency of binge and purge days (i.e., days during which at least one binge-eating or purging episode occurred; $P = 0.004$) (Hedges *et al.* 2003; Hoopes *et al.* 2003). Binge-eating/purging remission rates were 32% for topiramate and 6% for placebo (P = not significant). Dropout rates were 34% for topiramate and 47% for placebo. In the second study, subjects with DSM-IV bulimia nervosa received 10 weeks of topiramate (titrated to 250 mg/day in week 6; $n = 30$) or placebo ($n = 30$) (C. Nickel *et al.* 2005b). Topiramate was associated with significant decreases in binge/purge frequency (defined as a > 50% reduction; 37% for topiramate and 3% for placebo), body weight (difference in weight loss between the two groups, 3.8 kg), and scores on all of the 36-Item Short Form Health Survey subscales (all $P < 0.001$).

Binge-eating disorder. In the first controlled study in binge-eating disorder, 61 subjects with DSM-IV binge-eating disorder and obesity received topiramate or placebo for 14 weeks (McElroy *et al.* 2003). Topiramate was significantly superior to placebo in reducing binge-eating frequency as well as global severity of illness, obsessive-compulsive features of binge-eating symptoms, body weight, and BMI. The dropout rate, however, was high: 14 subjects (47%) receiving topiramate and 12 (39%) receiving placebo did not complete the trial.

The second controlled study of topiramate in binge-eating disorder was a multicenter trial in which subjects with DSM-IV binge-eating disorder and at least three binge-eating days per week, a BMI ranging from 30 to 50, and no current psychiatric disorders or substance

abuse were randomly assigned to topiramate or placebo for 16 weeks (McElroy *et al.* 2007). Of 407 subjects enrolled, 13 did not meet the inclusion criteria; 195 topiramate-and 199 placebo-treated subjects were therefore evaluated for efficacy. Topiramate significantly reduced the number of binge-eating days per week, the number of binge-eating episodes per week, weight, and BMI compared with placebo (all $P < 0.001$). The drug also significantly decreased measures of obsessive-compulsive symptoms, impulsivity, hunger, and disability. Fifty-eight percent of topiramate-treated subjects achieved remission, compared with 29% of placebo-treated subjects ($P < 0.001$). Discontinuation rates were 30% in each group; adverse events were the most common reason for topiramate discontinuation (16% vs. 8% for placebo).

The third controlled study of topiramate in binge-eating disorder was another multicenter trial, in which 73 patients with binge-eating disorder and obesity were randomly assigned to 19 sessions of cognitive-behavioral therapy in conjunction with topiramate or placebo for 21 weeks (Claudino *et al.* 2007). Compared with patients given placebo, those given topiramate showed a significantly greater rate of reduction in weight (the primary outcome measure) over the course of treatment ($P < 0.001$). Topiramate recipients also showed a significant weight loss ([?] 6.8 kg) relative to placebo recipients ([?] 0.9 kg). A greater percentage of topiramate-treated patients (31 of 37 [84%]) attained remission of binge eating compared with placebo-treated patients (22 of 36 [61%]; $P = 0.03$). There was no difference in completion rates between groups, although one topiramate recipient withdrew because of an adverse effect.

Phentermine-topiramate for binge-eating disorder and bulimia nervosa.

In a randomized controlled trial, 22 patients with bulimia nervosa ($n = 4$) or binge-eating disorder ($n = 18$) were randomly assigned to 12 weeks of phentermine-topiramate (23 mg per 3.75 mg/day to 92 mg per 15 mg/day) or placebo, followed by a 2-week drug washout and then a 12-week crossover (Safer *et al.* 2020). The number of binge-eating days per month decreased from 16.2 at baseline to 4.2 after phentermine-topiramate versus 13.2 after placebo ($P < 0.0001$). Weight loss was greater with phentermine-topiramate ([?] 5.8 kg) than placebo (+ 0.4 kg). Dropout rates were low (9% for both treatment arms), with few side effects.

Sleep-related eating disorder. In the randomized controlled trial of topiramate in sleep-related eating disorder, 34 patients experiencing three or more sleep-related eating episodes per week were randomly assigned to topiramate ([?] 300 mg/day) or placebo for 13 weeks (Winkelman *et al.* 2020). Topiramate was superior to placebo for reducing sleep-related eating episodes ($P = 0.035$) and was associated with a higher rate of global response (71% for topiramate vs. 27% for placebo; *P* = 0.016). The topiramate group also lost significantly more weight ([?] 8.5 lb vs. + 1.0 lb; *P* = 0.001). However, the drug was not well tolerated, with paresthesia and cognitive dysfunction being the most common side effects. Although it is classified as a parasomnia in DSM-5 (American Psychiatric Association 2013), sleep-related eating disorder shares phenomenological features with night eating syndrome, which DSM-5 lists as an "other specified feeding or eating disorder." Indeed, there are case reports of topiramate being helpful for individuals with night eating syndrome (Kucukgoncu *et al.* 2015).

Other eating and feeding disorders. Currently, there are no randomized controlled studies of topiramate in anorexia nervosa, pica, rumination disorder, or avoidant/restrictive

food intake disorder. However, there are reports of topiramate triggering or worsening anorexia nervosa as well as patients with eating disorders misusing the drug to lose weight (McElroy *et al.* 2008). Conversely, there is one case report of topiramate being helpful for pica (Pena-Salazar and Kazah 2020). Finally, although hyperphagia is not classified as an eating or feeding disorder, one randomized controlled trial showed that topiramate was superior to placebo for reducing hyperphagia in patients with Prader-Willi syndrome (*N* = 62 [Consoli *et al.* 2019]).

Substance-Related and Addictive Disorders

Growing evidence suggests that topiramate may have therapeutic effects in some substance use and addiction disorders, especially alcohol use disorder.

Alcohol use disorder. At least 12 randomized placebo-controlled studies have examined topiramate in alcohol use disorder. In the first study, 150 subjects with DSM-IV alcohol dependence were randomly assigned to topiramate ([?] 300 mg/day) or placebo for 12 weeks (Johnson *et al.* 2003). All participants also received compliance enhancement therapy. At study end, subjects receiving topiramate had significantly fewer drinks per day (*P* = 0.0006), fewer drinks per drinking day (*P* = 0.0009), fewer heavy drinking days (*P* = 0.0003), more days abstinent (*P* = 0.0003), and a log plasma g-glutamyl transferase ratio of 0.07 less ([?] 0.11 to [?] 0.02; *P* = 0.0046) compared with those receiving placebo. Craving was also significantly more improved with topiramate than with placebo.

In the second study, 371 subjects with DSM-IV alcohol dependence were randomly assigned to topiramate ([?] 300 mg/day) or placebo, along with a weekly compliance enhancement intervention, at 16 sites for 14 weeks (Johnson *et al.* 2007). Topiramate was significantly superior to placebo in reducing the percentage of heavy drinking days and other drinking outcomes (e.g., drinks per drinking day), increasing the percentage of days abstinent, and improving the log plasma g-glutamyl transferase ratio (all *P* [?] 0.002).

In the third study, 155 individuals with DSM-IV alcohol dependence who had been detoxified for 1 week were randomly assigned to topiramate ([?] 300 mg/day), naltrexone, or placebo in addition to relapse prevention counseling and encouragement to participate in Alcoholics Anonymous for 12 weeks (Baltieri *et al.* 2008). Topiramate was superior to placebo for time to first relapse, cumulative abstinence duration, weeks of heavy drinking, and percentage of subjects abstinent at 4 and 8 weeks (but not at 12 weeks). There were no significant differences between naltrexone and placebo or between topiramate and naltrexone.

In the fourth study, 63 patients with DSM-IV alcohol dependence were randomly assigned to topiramate or placebo for 12 weeks (Rubio *et al.* 2009). Compared with placebo recipients, topiramate recipients had significantly lower numbers of drinks per drinking day ($P < 0.05$) and of heavy drinking days ($P < 0.001$).

In the fifth study, 170 subjects with comorbid DSM-IV alcohol and cocaine dependence who had attained baseline abstinence were randomly assigned to topiramate (300 mg/day) or placebo in addition to weekly psychotherapy for 13 weeks (Kampman *et al.* 2013). Topiramate was not superior to placebo in reducing alcohol or cocaine use.

In the sixth study, 106 patients with DSM-IV alcohol dependence receiving residential treatment were randomly assigned to topiramate (100-300 mg/day) or placebo for 12 weeks (Likhitsathian *et al.* 2013). No significant differences between the two groups were found in mean percentages of heavy drinking days or time to first day of heavy drinking.

In the seventh study, 138 individuals with heavy drinking (most of whom had symptoms meeting DSM-IV criteria for alcohol dependence) were randomly assigned to topiramate (titrated to 100 mg bid) or placebo for 12 weeks (Kranzler *et al.* 2014). Compared with placebo, topiramate was associated with significantly greater reductions in heavy drinking days and increases in abstinent days ($P = 0.001$ and 0.03, respectively). Moreover, a single-nucleotide polymorphism (rs2832407) in *GRIK1*, which encodes for kainite glutamate receptor subunit GluK1, may have moderated topiramate's effect on heavy drinking. Specifically, topiramate's effect on heavy drinking days was significantly greater than that of placebo only in participants who were rs2832407 C-allele homozygotes.

In the eighth study, 30 veterans with PTSD and a co-occurring alcohol use disorder were randomly assigned to topiramate ([?] 300 mg/day) or placebo for 12 weeks (Batki *et al.* 2014). Compared with placebo, topiramate showed a greater tendency to reduce the primary outcome measure--frequency of drinking days ($P = 0.063$)--but not measures of PTSD symptoms.

In the ninth study, 85 participants with DSM-IV alcohol dependence were randomly assigned to topiramate, zonisamide, levetiracetam, or placebo for 14 weeks (including a 2-week taper period [Knapp *et al.* 2015]). Both topiramate and zonisamide produced significant reductions in drinking behavior. Topiramate and zonisamide both were associated with modest reductions in verbal fluency and working memory, but only topiramate produced a significant increase in mental slowing.

In the tenth study, 12 patients with bipolar disorder and an alcohol use disorder were randomly assigned to topiramate or placebo for 12 weeks (Sylvia *et al.* 2016). Topiramate performed poorly. Only two of five topiramate recipients completed the trial, compared with five of seven placebo recipients. In addition, topiramate did not improve drinking behavior and was poorly tolerated.

In the eleventh study, 32 veterans with alcohol use disorder and concussive symptoms from mild traumatic brain injury were randomly assigned to flexible-dosage topiramate or placebo for 12 weeks (Pennington *et al.* 2020). Alcohol use and concussive symptoms improved in both groups. Among completers, there was a greater reduction of alcohol use among veterans receiving topiramate.

The twelfth study analyzed functional MRI on alcohol cue-elicited brain responses, craving, and heavy drinking from 12 individuals with DSM-5 alcohol use disorder randomly assigned to topiramate (maximum dosage = 200 mg/day) or placebo for 12 weeks (Wetherill *et al.* 2021). Relative to placebo, topiramate produced greater reductions in alcohol cue activation of the left ventral striatum, bilateral orbitofrontal cortex, and medial orbitofrontal cortex as well as in alcohol cue-elicited craving and heavy drinking days.

Cocaine use disorder. At least six randomized placebo-controlled trials have evaluated topiramate in cocaine dependence, with mixed results. In the first study, 40 cocaine-dependent individuals were randomly assigned to topiramate (titrated gradually over 8 weeks to 200 mg/day) or placebo for 13 weeks (Kampman *et al.* 2004). Topiramate-treated subjects were more likely than placebo-treated subjects to be abstinent

from cocaine after week 8 ($P = 0.01$). They were also more likely to achieve 3 weeks of continuous abstinence from cocaine ($P = 0.05$).

In the second study, 81 cocaine-dependent subjects were randomly assigned to topiramate (titrated to 150 mg bid) plus mixed amphetamine salts or placebo for 12 weeks (Mariani *et al.* 2012). The proportion of patients achieving 3 weeks of abstinence was larger for active drug treatment (33.3%) than for placebo (16.7%). Combination treatment may also have been more effective in subjects with a high baseline frequency of cocaine use.

In the third study, 142 patients with DSM-IV cocaine dependence were randomly assigned to topiramate (target maintenance dosage = 300 mg/day) or placebo in combination with cognitive-behavioral therapy for 12 weeks (Johnson *et al.* 2013). Topiramate was more efficacious than placebo at increasing the weekly proportion of nonuse days. It also was associated with significantly more urinary cocaine-free weeks, decreased craving, and improved global functioning.

In the fourth trial, 170 subjects with comorbid DSM-IV cocaine and alcohol dependence were randomly assigned to topiramate 300 mg/day or placebo for 13 weeks (Kampman *et al.* 2013). Topiramate was not superior to placebo for reducing cocaine or alcohol use.

In the fifth study, 171 cocaine-dependent patients undergoing methadone maintenance treatment were randomly assigned to topiramate or placebo in addition to monetary voucher incentives that were either contingent or noncontingent on drug abstinence for 15 weeks (including 8 weeks at a maintenance dosage of 300 mg/day [Umbricht *et al.* 2014]). There were no significant differences between the topiramate and placebo conditions or between the contingent and noncontingent incentive conditions. In addition, there were no topiramate-contingency interactions, and topiramate was associated with cognitive impairment.

In the sixth trial, 127 adults with cocaine use disorder were randomly assigned to the combination of topiramate and mixed amphetamine salts or placebo for 12 weeks (Levin *et al.* 2020). The proportion of patients achieving 3 consecutive weeks of abstinence (the primary outcome) was significantly higher in the active drug group (14%) versus the placebo group (0%; $P = 0.03$). However, 20% of patients in the active drug group were discontinued from study medication.

Methamphetamine use disorder. At least two randomized controlled trials have assessed topiramate in methamphetamine addiction. In the first study, 140 subjects with methamphetamine addiction were randomly assigned to topiramate (target maintenance dosage = 200 mg/day) or placebo for 13 weeks (Elkashef *et al.* 2012). Topiramate did not increase abstinence from methamphetamine over weeks 6-12 of treatment (the primary outcome measure). On secondary outcomes, however, topiramate reduced weekly median urine methamphetamine levels and overall severity of dependence scores ($P = 0.03$ for both).

In the second study, 62 adults with DSM-IV methamphetamine dependence were randomly assigned to topiramate ([?] 200 mg/day) or placebo for 10 weeks (Rezaei *et al.* 2016). At week 6, the topiramate group had a significantly lower proportion of methamphetamine-positive urine test results ($P = 0.01$) compared with the placebo group. Topiramate-treated subjects also had lower scores on the drug use severity and drug need items on the Addiction Severity Index (both $P < 0.001$).

Smoking cessation. At least four randomized placebo-controlled trials have assessed topiramate in smoking cessation. In the first study, topiramate was superior to placebo for abstinence from smoking in 94 subjects with comorbid DSM-IV alcohol dependence (Johnson *et al.* 2005). This 2005 study was a subgroup analysis of the first controlled study of topiramate in alcohol dependence (Johnson *et al.* 2003). In the second study, topiramate was superior to placebo for smoking cessation in male ($n = 38$) but not female ($n = 49$) individuals who had no associated psychopathology (Anthenelli *et al.* 2008). In the third study, which followed a placebo-controlled trial (Baltieri *et al.* 2008) in 155 male outpatients with alcohol dependence (according to ICD-10 criteria [World Health Organization 1992]), a subset of the participants with alcoholism who were smokers ($n = 103$) were randomly assigned to topiramate, naltrexone, or placebo for 12 weeks (Baltieri *et al.* 2009). Whereas naltrexone did not separate from placebo, topiramate was more effective than placebo in reducing the number of cigarettes smoked. In the fourth trial, 129 smoking-and alcohol-abstinent men with alcohol dependence were randomly assigned to topiramate ([?] 200 mg/day) or placebo for 12 weeks (Anthenelli *et al.* 2017). Topiramate had no effect on smoking cessation or alcohol relapse prevention.

Of note, the authors of a systematic review and meta-analysis including these trials concluded that there was not sufficient evidence favoring topiramate over placebo for smoking cessation (Lotfy *et al.* 2020).

Gambling disorder. Topiramate has been evaluated in two randomized placebo-controlled trials in gambling disorder, with mixed results. In the first study, 42 patients with DSM-IV pathological gambling received either topiramate or placebo for 14 weeks (Berlin *et al.* 2013). There were no significant treatment effects of topiramate on the primary outcome (Yale-Brown Obsessive Compulsive Scale [Y-BOCS] adapted for Pathological

Gambling) or any secondary outcome measures. In the second study, 30 participants with gambling disorder were randomly assigned to topiramate or placebo for 12 weeks (de Brito *et al.* 2017). All participants also received a brief cognitive intervention. Topiramate was superior to placebo in reducing gambling craving (*P* = 0.017), time and money spent gambling (*P* = 0.007 and 0.047, respectively), and cognitive distortions related to gambling (*P* = 0.003). Topiramate also improved social adjustment but had no effect on depression or impulsivity.

Posttraumatic Stress Disorder

Topiramate has been evaluated in at least four randomized placebo-controlled studies in PTSD. In the first study, 38 civilian patients with PTSD were randomly assigned to flexible dosages of topiramate (median = 150 mg/day) or placebo for 12 weeks (Tucker *et al.* 2007). No significant difference between topiramate and placebo was found on the primary efficacy measure, change in total Clinician-Administered PTSD Scale (CAPS) score. However, significant reductions in favor of topiramate were observed for the Eight-Item Treatment Outcome Posttraumatic Stress Disorder Scale score, with a decrease in overall severity of 68% for topiramate versus 42% for placebo (*P* = 0.025).

In the second study, 40 male veterans with chronic PTSD, most of whom were receiving antidepressants, were given topiramate ([?] 200 mg/day) or placebo for 7 weeks (Lindley *et al.* 2007). No significant drug-versus-placebo differences were found for the primary outcome measures (i.e., scores on the CAPS, Clinical Global Impression Scale Severity of Illness subscale, or Patient Global Impression of Improvement Scale).

In the third study, 70 civilian patients with PTSD were randomly assigned to receive topiramate (mean dosage = 102.94 mg/day) or placebo for 12 weeks (Yeh *et al.* 2011). Compared with placebo recipients, topiramate recipients showed significantly greater improvement in both re-experiencing and avoidance/numbing symptoms as measured with the

CAPS (*P* = 0.04 and 0.0001, respectively) as well as a significant reduction in CAPS total scores (*P* = 0.0076). Topiramate was generally well tolerated.

In the fourth study, 30 veterans with PTSD and a co-occurring alcohol use disorder were randomly assigned to topiramate ([?] 300 mg/day) or placebo for 12 weeks (Batki *et al.* 2014). Compared with placebo, topiramate showed a greater tendency to reduce drinking frequency (the primary measure; *P* = 0.063) but had no effect on PTSD symptom measures.

At least two meta-analyses including these studies have been published. The first was a meta-analysis of topiramate as monotherapy or adjunctive therapy for PTSD, in which the authors concluded that topiramate produced a small but significant reduction in hyperarousal symptoms (*P* = 0.033) but did not reduce re-experiencing or avoidance symptoms (Varma *et al.* 2018). The second was a network meta-analysis, in which the authors concluded that topiramate was superior to placebo for decreasing PTSD symptoms and should be viewed as an effective treatment option for PTSD (de Moraes Costa *et al.* 2020).

Obsessive-Compulsive Disorder

Four randomized placebo-controlled trials have evaluated adjunctive topiramate in individuals with OCD, with mixed results. In the first study, 41 patients with OCD that had not improved after at least 12 weeks of treatment with an SSRI were randomly assigned to receive topiramate or placebo plus their current OCD regimen for 12 weeks. Recipients of topiramate showed a mean decrease of 32% in Y-BOCS scores, whereas placebo recipients had a decrease of 2.4% (Mowla *et al.* 2010). In the second study, adjunctive topiramate (mean endpoint dosage = 179 mg/day) significantly reduced Y-BOCS Compulsions subscale scores (*P* = 0.014) but not Obsessions subscale scores or total scores for 36 adults with OCD receiving an SSRI (Berlin *et al.* 2011). In the third study, 39 inpatients with OCD and bipolar mania were randomly assigned to have topiramate or placebo added to their current regimen of lithium, olanzapine, and clonazepam for 4 months (Sahraian *et al.* 2014). Y-BOCS scores showed a greater numeric decline for patients receiving placebo than for those receiving topiramate. By contrast, among the 32 completers, there were significantly more responders (defined as a > 34% reduction in Y-BOCS scores) among topiramate recipients than among placebo recipients (53% vs. 12.5%, respectively; $P < 0.01$). However, in the fourth study involving 38 patients with refractory OCD, topiramate (mean dosage = 137.5 mg/day) was not superior to placebo in reducing Y-BOCS scores after 12 weeks of treatment (Afshar *et al.* 2014).

Borderline Personality Disorder

Three randomized placebo-controlled studies conducted by the same group evaluated topiramate in DSM-IV-defined borderline personality disorder (Loew *et al.* 2006; M. K. Nickel *et al.* 2004, 2005a). In the first study, 29 female subjects were randomly assigned (2:1) to topiramate or placebo for 8 weeks (M. K. Nickel *et al.* 2004). The topiramate dosage was increased to 250 mg/day over 6 weeks. At study end, significantly

greater improvement on four subscales of the State-Trait Anger Expression Inventory (state-anger, trait-anger, anger-out, and anger-control) was observed for topiramate-treated participants compared with placebo.

In the second study, 42 male subjects with borderline personality disorder received topiramate or placebo for 8 weeks (M. K. Nickel *et al.* 2005a). As in the study in female subjects, significantly greater improvement on the same four State-Trait Anger Expression Inventory subscales was found for male subjects treated with topiramate compared with placebo.

In the third study, 56 women with borderline personality disorder received topiramate or placebo for 10 weeks (Loew *et al.* 2006). Topiramate was titrated to 200 mg/day over 6 weeks and then held constant. Topiramate was superior to placebo on the somatization, interpersonal sensitivity, anxiety, hostility, phobic anxiety, and Global Severity Index subscales of the Symptom Checklist-90 Revised (all $P < 0.001$), all eight scales of the 36-Item Short Form Health Survey (all $P < 0.01$), and four of eight scales of the Inventory of Interpersonal Problems (all $P < 0.001$). In all three studies, topiramate was well tolerated, and there were no psychotic or suicidal adverse events.

Impulse-Control Disorders

Case reports and open studies suggest that topiramate might be effective in various impulse-control disorders, including intermittent explosive disorder (Yulug *et al.* 2016), kleptomania (Dannon 2003; Kaplan 2007), pyromania (Grant 2006), trichotillomania (Lochner *et al.* 2006), and excoriation (skin-picking) disorder (Jafferany and Osuagwu 2017). However, in a randomized controlled trial in 50 patients with compulsive buying disorder, topiramate was similar to placebo on the primary outcome, the Y-BOCS-Shopping Version (Nicoli de Mattos *et al.* 2020). Nonetheless, topiramate recipients did better than placebo recipients on the Compulsive Buying Follow-Up Scale, a secondary outcome measure.

Although no randomized controlled trial to date has evaluated topiramate in the treatment of intermittent explosive disorder, a systematic review concluded that topiramate might be effective and well tolerated in the treatment of individuals with anger or aggression (Varghese *et al.* 2010). Of note, the studies included in this review evaluated topiramate in the treatment of anger or aggression in individuals with borderline personality disorder, major depressive disorder, or low back pain--conditions with an unclear relationship with intermittent explosive disorder.

Paraphilias

Several case reports suggest that topiramate may be effective in individuals with paraphilias (Wan *et al.* 2019), including fetishism (Shiah *et al.* 2006) and exhibitionism (Bell 2012). There is also one case report of the successful treatment of compulsive sexual behavior with topiramate (Bell 2012).

Psychotropic Medication-Associated Weight Gain

At least five randomized placebo-controlled studies have suggested that topiramate reduces antipsychotic-related weight gain in patients with psychotic or mood disorders. In the first study, 66 inpatients with schizophrenia receiving antipsychotic medication and "carrying excess weight" were randomly assigned to topiramate (100 or 200 mg/day) or placebo for 12 weeks (Ko *et al.* 2005). Body weight, BMI, and waist

and hip circumferences decreased significantly in the group that received topiramate 200 mg/day compared with those that received topiramate 100 mg/day or placebo.

In the second study, 43 women with mood or psychotic disorders who had gained weight while taking olanzapine were given topiramate or placebo for 10 weeks (M. K. Nickel *et al.* 2005b). Weight loss was significantly greater (by 5.6 kg) in the topiramate group. Topiramate-treated subjects also experienced significantly greater improvement in measures of health-related quality of life and psychological impairment.

In a third study, topiramate as an adjunct to lithium or valproate treatment was ineffective for manic symptoms in patients with bipolar I disorder experiencing a manic or mixed episode. However, topiramate was associated with significantly greater reductions in body weight ([?] 2.5 vs. 0.2 kg; $P < 0.001$) and BMI ([?] 0.84 vs. 0.07; $P < 0.001$) versus placebo (Roy Chengappa *et al.* 2006).

In the fourth study, adjunctive topiramate was evaluated for utility in the prevention of olanzapine-related weight gain (Narula *et al.* 2010). In this 12-week trial, 72 patients with schizophrenia were randomly assigned to olanzapine plus topiramate 100 mg or olanzapine plus placebo. Whereas topiramate augmentation was associated with statistically significant weight loss, placebo-augmented olanzapine was associated with significant weight gain ($P = 0.05$ between-group difference). Topiramate augmentation was also associated with significantly greater improvement in several metabolic variables, systolic and diastolic blood pressure, and PANSS General Psychopathology Scale score and total score.

In the fifth study, 68 individuals with bipolar disorder or schizophrenia hospitalized and treated with olanzapine were randomly assigned to one of the following four treatment groups for 12 weeks: placebo or topiramate 50, 100, or 200 mg/day (Talaei *et al.* 2016). Topiramate at all three dosages was superior to placebo in preventing weight gain. There were no differences, however, among the three topiramate dosages.

Of note, several reviews and meta-analyses have evaluated pharmacological interventions for psychotropic-induced weight gain. Most have concluded that topiramate reduced body weight. For example, in a meta-analysis of pharmacological interventions in weight gain management in patients with severe mental illness, which included the topiramate trials just described, the authors concluded that topiramate was efficacious and safe for weight reduction in this patient group (Hiluy *et al.* 2019). In a meta-review of meta-analyses of randomized controlled trials in patients from 15 studies of topiramate in schizophrenia, the authors concluded that topiramate had a "medium" effect size for weight reduction (Vancampfort *et al.* 2019).

Side Effects and Toxicology

The side-effect profile of topiramate may vary with the patient's illness, mood state, and concomitant medications.

Common Side Effects

The most common side effects of topiramate in initial dose-ranging studies in patients with epilepsy when used in combination with other antiepileptic drugs at dosages of 200-1,000 mg/day were related to the CNS. These side effects included dizziness, somnolence, psychomotor slowing, nervousness, paresthesias, ataxia, difficulty with memory, difficulty with concentration or attention, confusion, and speech disorders or related speech problems (Langtry *et al.* 1997; Shorvon 1996). Other side effects were nystagmus, depression, nausea, diplopia, abnormal vision, anorexia, language problems, and tremor. When topiramate was used as monotherapy in patients with epilepsy, the most common side effects were dizziness, anxiety, paresthesias, insomnia, somnolence, myalgia, anorexia, nausea, dyspepsia, and diarrhea. The most common side effects of topiramate in the large registration trials for migraine headache (which used total dosages of 50, 100, and 200 mg/day) were paresthesias, fatigue, memory difficulties, concentration or attention problems, and mood problems (Bussone *et al.* 2006). In the monotherapy trials in adult mania, paresthesias, decreased appetite, dry mouth, and weight loss were more common with topiramate than placebo (Kushner *et al.* 2006). In the obesity trials, events related to the CNS, peripheral nervous system, or psychiatric disorders were most commonly reported (Rosenstock *et al.* 2007). These included paresthesias, fatigue, taste perversion, anorexia, and difficulty with attention, concentration, and/or memory. Overall, paresthesias and cognitive complaints were the most troublesome adverse events (van Passel *et al.* 2006). A meta-analysis suggested that a dose-response relationship exists for dizziness, cognitive impairment, and fatigue (Zaccara *et al.* 2008).

The CNS and gastrointestinal effects of topiramate are usually mild to moderate in severity and often decrease or resolve with time or dosage reduction (Meador *et al.* 2003; Shorvon 1996). In addition, they may be minimized through slow titration of topiramate dosage (Biton *et al.* 2001). However, topiramate may be associated with greater cognitive impairment than some of the other new antiepileptic drugs (Martin *et al.* 1999; Meador *et al.* 2003).

Infrequent Adverse Effects

Infrequent but serious side effects of topiramate include nephrolithiasis, an ocular syndrome of acute myopia with secondary angle-closure glaucoma, oligohydrosis and hyperthermia, and metabolic acidosis (van Passel *et al.* 2006). Mild hypokalemia, which usually is not clinically significant, may also occur in about 10% of topiramate recipients (Dell'Orto *et al.* 2014).

The incidence of topiramate-associated nephrolithiasis has been estimated to be 1.5% (Shorvon 1996). In the epilepsy trials, more than 75% of the patients who developed kidney stones elected to continue treatment with topiramate (Reife *et al.* 2000). Nephrolithiasis is thought to be related to topiramate's inhibition of carbonic anhydrase in the kidney (Welch *et al.* 2006).

The secondary angle-closure glaucoma associated with topiramate is characterized by acute onset of bilateral blurred vision and ocular pain (Fraunfelder 2004; Fraunfelder *et al.* 2004). Ophthalmological findings include bilateral myopia, conjunctival hyperemia, anterior chamber shallowing, and increased intraocular pressure. Most cases have occurred within 1 month of topiramate initiation and fully resolved with drug discontinuation. Peripheral iridectomy and laser iridotomy are not effective. The syndrome has been attributed to sulfamate-induced ciliary body edema.

Oligohydrosis and hyperthermia occurring with topiramate can present as heat stroke or fever, may be related to exercise or high environmental temperature, can be fatal, are probably more common in children than in adults, and are reversible upon drug discontinuation (Karachristianou *et al.* 2013). Topiramate-induced metabolic acidosis is usually asymptomatic and associated with low bicarbonate and, to a lesser degree, increased chloride levels (Dell'Orto *et al.* 2014; Sciegienka *et al.* 2015). Rarely, it presents with Kussmaul breathing or even altered mental status. Topiramate-induced metabolic acidosis may be due to the carbonic anhydrase-inhibiting properties of topiramate, and it is also reversible on drug discontinuation.

Because there were no clinically relevant changes in hepatic, renal, or hematological parameters in the registration trials of topiramate, laboratory monitoring was initially thought to be unnecessary (Reife *et al.* 2000; Sachdeo *et al.* 2002). In addition, no treatment-related changes were noted in physical or neurological examinations (except body weight loss), electrocardiograms, or ophthalmological or audiometric test results. However, because topiramate may cause metabolic acidosis and hypokalemia in some patients, it is now recommended that baseline and periodic serum bicarbonate and potassium levels be measured in patients receiving topiramate (Dell'Orto *et al.* 2014; Sachdeo *et al.* 2002; van Passel *et al.* 2006; Welch *et al.* 2006).

Psychiatric Adverse Events

A growing concern is the psychiatric adverse-event profile of antiepileptic drugs in patients with epilepsy, including the question of whether such drugs cause depression, suicidality, psychosis, or aggression (Dussaule and Bouilleret 2018). Thus, topiramate may be associated with depression in patients with epilepsy, especially during rapid titration (Mula and Sander 2007). There are also isolated reports of topiramate's induction of mood and anxiety symptoms in psychiatric patients (Damsa *et al.* 2006; Duan *et al.* 2019; Klufas and Thompson 2001). Moreover, one obesity study reported eight (6.2%) suicide-related events occurring in topiramate-treated subjects versus none in placebo-treated subjects (Rosenstock *et al.* 2007).

Use in Pregnancy

Topiramate can cause fetal harm when given to pregnant women. Prenatal exposure to topiramate is associated with an increased risk of oral clefts (Alsaad *et al.* 2015; Hunt *et al.* 2008). Topiramate might also contribute to other birth defects, including neural tube defects, when used in combination with other antiepileptics, especially valproate (Vajda *et al.* 2019).

Drug-Drug Interactions

The clearance of topiramate can be increased by coadministration of hepatic enzyme-inducing drugs (Bialer *et al.* 2004; Gidal 2002; Langtry *et al.* 1997; Rosenfeld *et al.* 1997; van Passel *et al.* 2006). Thus, carbamazepine and phenytoin may substantially decrease topiramate levels.

Conversely, topiramate has mild enzyme-inducing properties and may enhance the metabolism of ethinyl estradiol. Available data suggest that this induction is insignificant at topiramate dosages of 200 mg/day or less, but induction becomes dose

dependent at dosages greater than 200 mg/day and occurs to a great extent (Bialer *et al.* 2004). Therefore, women taking combination oral contraceptive agents must be counseled about this potential interaction.

Although there have been reports of topiramate causing increased lithium levels (Abraham and Owen 2004), this effect appears to be only rarely clinically significant (Bialer *et al.* 2004).

Conclusion

In summary, although topiramate does not have regulatory approval for use in the treatment of psychiatric disorders, considerable data suggest that this drug may be helpful for a wide range of psychiatric conditions. Topiramate appears efficacious in binge-eating disorder, bulimia nervosa, psychotropic-associated weight gain, and possibly alcohol use disorders. It might also be efficacious for major depressive disorder, schizophrenia, borderline personality disorder, and PTSD. Data on topiramate's efficacy in cocaine or methamphetamine use disorders, smoking cessation, and OCD have been mixed. Of note, there is no evidence to suggest that topiramate has acute antimanic or long-term mood-stabilizing effects in bipolar disorder. The use of topiramate in psychiatric disorders, however, is limited by its adverse-event profile.

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Other Agents

CHAPTER 43

Agents for Neurocognitive Disorders

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Neurocognitive disorder is an umbrella term referring to the heterogeneous and complex disruption of cellular function leading to loss of synaptic plasticity, cell death, gliosis, inflammation, and disruption of the functional networks underlying cognition (Amarapurkar *et al.* 1995; Brun *et al.* 1995; Crews and Masliah 2010; Elahi and Miller 2017; Malik *et al.* 2007; Olajide *et al.* 2021). According to DSM-5 (American Psychiatric Association 2013), a diagnosis of neurocognitive disorder requires a decline from a previous level in at least one area of functioning regarding complex attention, executive function, learning and memory, language, perceptual-motor skills, or social cognition.

Neurocognitive disorders are currently classified based on clinical features, evolution over time, and underlying pathologies primarily categorized according to the accumulation of abnormal protein aggregates in neurons and glia in vulnerable areas of the brain, which can precede clinical manifestation by years (Elahi and Miller 2017; Seeley *et al.* 2009; Sorbi *et al.* 2012). The accuracy of diagnosis is increasingly being improved with the use of imaging, biofluid, and genetic biomarkers, even at times allowing for recognition of the disease process before symptoms are present (Elahi and Miller 2017). Intervention at a stage before irreversible damage occurs would be optimal. Unfortunately, there is currently no clear evidence that any pharmacological intervention can prevent the onset and progression of a major neurocognitive disorder, although several strategies continue to be investigated for possible disease-modifying effects. Aducanumab and lecanemab, the medications most recently approved by the FDA for Alzheimer's disease, lower amyloid b (Ab) plaque levels in the brain. Thus, these are the first FDA-approved drugs to claim an effect on the Alzheimer's disease process.

In this chapter we describe aducanumab, lecanemab, and the other FDA-approved pharmacological approaches proven to provide modest symptomatic relief for certain neurocognitive disorders. In addition, we briefly review other treatments that have been found to provide no benefit and additional future treatments that may hold promise.

Amyloid-Targeted Therapies

Ab plaques and neurofibrillary tangles have been the neuropathological hallmarks of Alzheimer's disease. Tangles are filamentous inclusions of aggregates of misfolded and hyperphosphorylated tau proteins that accumulate intraneuronally. Ab peptides are the product of sequential proteolytic processing of amyloid precursor protein by the enzymes b-secretase and g-secretase. These peptides assemble into insoluble b-fibrillar aggregates that deposit extracellularly in the brain parenchyma and cerebral vasculature (Bloom 2014; Decourt *et al.* 2021; Fowler *et al.* 2006; Love *et al.* 2009; Serrano-Pozo *et al.* 2011). The presence of Ab and tau has been correlated with the progression of Alzheimer's disease, but the mechanism of their toxicity remains controversial and poorly understood. Some argue that Ab is intrinsically toxic, whereas others believe that it seeds the formation of tau tangles and leads to a cascade of pathologically toxic events (Chuang *et al.* 2018; Decourt *et al.* 2021; Guo and Lee 2014). Still others argue that Ab and tau may be produced as a reaction to or defense against neurodegeneration and cell death, making them questionable biomarkers and inappropriate drug targets (Lee *et al.* 2005; Mullane and Williams 2018a, 2018b; Ricciarelli and Fedele 2017). Despite the controversy and the lack of clarity, the pursuit of Ab clearance (or halting its production via secretase inhibitors) has dominated pharmacological investigations and has led to numerous randomized controlled trials. Many trial drugs have produced a measurable reduction or clearance of amyloid but have failed to bring about any substantial improvement in cognition (Table 43-1), further challenging the legitimacy of Ab as a target for drug development (Ackley *et al.* 2021; Long and Holtzman 2019; Penninkilampi *et al.* 2017; Stoiljkovic *et al.* 2021; Uddin *et al.* 2020; van Dyck 2018; Vaz and Silvestre 2020).

TABLE 43-1. Some of the major clinical trials of amyloid-targeted pharmaceutical treatments

Drug name	Sponsor	Status	Mechanism of action	Positive outcomes	Negative outcomes	Referenc
AN-1792	Pfizer/Janssen	Phase II terminated	Active immunotherapy	Reduced CSF p-tau; cognitive benefit at 4.6-year follow-up	Increased brain atrophy; increased risk of meningoencephalitis and death	Orgogoz *al.* 20
CAD106	Novartis/ Amgen	Phase II/III terminated	Active immunotherapy	Reduced CSF p-tau	Increased risk of ARIAs	Lopez e 2019
ACC001	Pfizer/Janssen	Phase II terminated	Active immunotherapy	Sustained immune response	No cognitive or functional improvement; skin lesions	Hull *et a* 2017
Affitope AD02	AFFiRiS	Phase II terminated	Active immunotherapy	Cognitive improvement, slowed hippocampal atrophy in a control group	Failed to reach primary cognitive endpoints	Schneeb *et al.*
ABvac40	Araclon Biotech	Phase II active	Active immunotherapy	Sustained immune response	Increased risk of ARIAs	AlzForu 2020
UB-311	United Neuroscience	Phase II terminated	Active immunotherapy	Modest reduction in brain Ab	Failed to reach cognitive and functional endpoints	Alzheim News Today 2019
Bapineuzumab	Pfizer/Janssen	Phase III terminated	Passive immunotherapy	Reduced CSF p-tau	Increased risk of ARIAs; no cognitive improvement	Salloway *al.* 20
Solanezumab	Eli Lilly	Phase III terminated	Passive immunotherapy	Some cognitive improvement in	Failed to reach cognitive and functional endpoints	Doody e 2014; Honig *al.* 20

Note. Ab = amyloid b; AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormality; CSF = cerebrospinal fluid; MCI = mild cognitive impairm tau = phosphorylated tau.

Drug name	Sponsor	Status	Mechanism of action	Positive outcomes	Negative outcomes	Referenc
				patients with mild AD		
Ponezumab	Rinat Neuroscience/Pfizer	Phase II completed	Passive immunotherapy	No ARIA or encephalitis	Failed to reach primary cognitive endpoints	Landen 2017
Gantenerumab	Hoffmann-La Roche	Phase III terminated, reactivated	Passive immunotherapy	Nonsignificant benefit in patients with rapid clinical progression, post hoc analysis; reduction in brain Ab with high doses	Risk of ARIAs; Phase II halted after futility analysis; failed to reach primary endpoints with initial analysis	Ostrowit et al.
Aducanumab	Biogen	Phase III; FDA-approved and active	Passive immunotherapy	Significant benefit in cognitive measures with high doses, post hoc analysis; reduction in brain Ab, CSF p-tau	Risk of ARIAs; halted after futility analysis; failed to reach primary endpoints with initial analysis	Alexand al. 20
Lecanemab	Eisai/Biogen	Phase III; FDA-approved and active	Passive immunotherapy	Significant benefit in cognitive measures with high doses	Risk of ARIAs; failed to reach primary endpoints with initial analysis	Swanso al. 20
Crenezumab	Hoffmann-La Roche	Phase III terminated, reactivated	Passive immunotherapy	Significant benefit in cognitive measures with high doses, post hoc analysis	Halted after futility analysis; failed to reach primary endpoints with initial analysis	Decourt al. 20
CTS-21166	CoMentis/Astellas	Phase I completed	b-Secretase inhibitor	Decreased levels of plasma Ab	Pharmaceutical collaboration terminated	Uddin e 2020
BI 1181181	Boehringer Ingelheim	Phase I complet	b-Secretase inhibitor	Dose-dependent	Low blood-brain penetration and	AlzForu 2015

Note. Ab = amyloid b; AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormality; CSF = cerebrospinal fluid; MCI = mild cognitive impairm tau = phosphorylated tau.

Drug name	**Sponsor**	**Status**	**Mechanism of action**	**Positive outcomes**	**Negative outcomes**	**Referenc**
		ed		decreased levels of plasma and CSF Ab	low oral bioavailability	
LY2886721	Eli Lilly	Phase I terminated	b-Secretase inhibitor	Reduced concentrations of cerebral Ab	Liver toxicity	Menting Claas 2014
RG7129	Roche	Phase I terminated	b-Secretase inhibitor	Decreased levels of plasma Ab	Liver toxicity	AlzForu 2013
Verubecestat	Merck	Phase III terminated	b-Secretase inhibitor	Decreased levels of CSF Ab	Worsened cognitive function	Egan *et* 2018, 2019
Elenbecestat	Eisai/Biogen	Phase II/III terminated	b-Secretase inhibitor	Decreased levels of CSF Ab	No significant improvement in cognition	Bowma Roger 2019
Umibecestat	Novartis/ Amgen	Phase II/III terminated	b-Secretase inhibitor	Decreased levels of CSF Ab	Worsened cognitive function; increased brain atrophy	Lopez *e* 2019
Lanabecestat	AstraZeneca/Eli Lilly	Phase III terminated	b-Secretase inhibitor	Decreased levels of plasma and CSF Ab	No cognitive or functional improvement	Wessels *al.* 20
Atabecestat	Janssen	Phase III terminated	b-Secretase inhibitor	Dose-dependent decreased levels of CSF p-tau	Worsened cognitive function; hepatoxicity	Henley *e* 2019
Semagacestat	Eli Lilly	Phase III completed	g-secretase inhibitor	Decreased levels of plasma Ab	Halted after futility analysis showed ineffectiveness; increased risk of skin infection, cancer	Doody *e* 2013
Avagacestat	Bristol-Myers Squibb	Phase II terminated	g-secretase inhibitor	Dose-dependent decreased levels of CSF Ab	ARIAs; gastrointestinal and dermatological side effects; worsened cognition	Coric *et* 2015
Begacestat	Pfizer	Phase I completed	g-secretase inhibitor	Decreased levels of plasma Ab	Gastrointestinal and dermatological side effects;	Stoiljko *al.* 20

Note. Ab = amyloid b; AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormality; CSF = cerebrospinal fluid; MCI = mild cognitive impairm tau = phosphorylated tau.

Drug name	**Sponsor**	**Status**	**Mechanism of action**	**Positive outcomes**	**Negative outcomes**	**Referenc**
					worsened cognition	
Tarenflurbil	Myrexis	Phase III terminated	g-secretase modulator	Slowing of decline in mild AD in Phase II	Failed to demonstrate any disease-modifying effect in Phase III	Green *et* 2009
Pioglitazone	Takeda/Zinfandel	Phase III terminated	Thiazolidinediones	Some cognitive improvement in MCI	Failed to demonstrate significant benefit	Miller *e* 2011
Rosiglitazone	GlaxoSmithKline	Phase III completed	Thiazolidinediones	Some cognitive improvement in MCI	Failed to demonstrate significant benefit	Miller *e* 2011
Scyllo-inositol	Elan	Phase II completed	Ab aggregation inhibitor	Decreased levels of CSF Ab	No cognitive or functional improvement; toxicity at higher doses	Sallowa *al.* 20
Tramiprosate	Bellus Health	Phase III completed	Ab aggregation inhibitor	Slowed hippocampal atrophy, post hoc analysis	No cognitive improvement	Aisen *et* 2011

Note. Ab = amyloid b; AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormality; CSF = cerebrospinal fluid; MCI = mild cognitive impairm
tau = phosphorylated tau.

Amyloid-Lowering Agents via Immunotherapy

The most extensively developed approach to removing Ab is through vaccination, which involves actively stimulating the production of endogenous antibodies as opposed to administering Ab as an antigen in order to elicit an immune response against it. Initial Alzheimer's treatment studies looking at antiamyloid immunization were considered failures because of severe side effects and the lack of significant clinical results (Gilman *et al.* 2005; Karran 2012; Pasquier *et al.* 2016; Ricciarelli and Fedele 2017). T cell-mediated meningoencephalitis was attributed to an early active vaccine (AN-1792) in 6% of patients (Gilman *et al.* 2005). Additional active vaccine studies showed improved safety and tolerability but have still failed to prove clinical efficacy.

In contrast to the limited number of studies that have investigated active immunization strategies, there has been significantly more investigation of passive immunization. Agents used in this approach are human or humanized monoclonal antibodies that bind with high affinity to aggregated Ab and promote its removal by Fc receptor-mediated phagocytosis, while showing lower affinity to monomers (Ricciarelli and Fedele 2017). Most passive immunotherapies that have reached Phase III trials were ineffective at the doses tested, failed to meet primary endpoints, and were associated with amyloid-related imaging abnormalities (ARIAs) such as edema and microhemorrhages at higher doses (Salloway *et al.* 2014). Clinical trials for gantenerumab and aducanumab were both halted after an interim futility analysis (Ostrowitzki *et al.* 2017; Sevigny *et al.* 2016). Both trials were then restarted after further analysis, with the latter agent now approved by the FDA. While lecanemab (also now FDA approved) failed to meet primary endpoints with the initial analysis (at 12 months), it did meet these endpoints with the final analysis (at 18 months). Lecanemab has been associated with increased risk for ARIAs.

Aducanumab

The FDA approved aducanumab on June 7, 2021, making it the first agent to be approved for the treatment of Alzheimer's disease since 2003. Aducanumab, a recombinant human immunoglobulin g monoclonal anti-Ab antibody that specifically targets Ab oligomers and fibrils (soluble and insoluble forms), was studied in two nearly identically designed Phase III double-blind, placebo-controlled randomized clinical trials of high and low doses (Sevigny *et al.* 2016). Although both studies were stopped for futility in March 2019, one showed clinical efficacy in reanalysis, specifically in participants treated with the higher dose and for longer periods (Alexander *et al.* 2021; Arndt *et al.* 2018; Sevigny *et al.* 2016). Reanalysis of the complete patient data showed that the one study had met its primary endpoint of slowing cognitive decline, measured via Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) scores. ^{18}F-florbetapir PET imaging showed evidence of amyloid reduction, and substudies of cerebrospinal fluid (CSF) showed a dose-related decrease in phosphorylated tau--a possible "downstream" effect of amyloid removal (Sabbagh and Cummings 2021). The accelerated FDA approval of aducanumab was contingent on verification of clinical benefit in a confirmatory trial or trials that will be allowed to run until 2030. People with early stages of Alzheimer's disease are the target population for treatment. Treatment is begun only after confirmation of an amyloid burden via ^{18}F-florbetapir PET imaging or CSF analysis.

Aducanumab (aducanumab-avwa) injection, for intravenous use, is marketed as single-use vials in strengths of 170 mg and 300 mg (Biogen Inc. 2023). Dosing is via intravenous infusion administered over approximately 1 hour every 4 weeks and at least 21 days apart. The target dose is 10 mg/kg and is reached after a titration schedule of six infusions.

Detection of the side effect of greatest concern for aducanumab--ARIAs with edema or microhemorrhage--requires monitoring with serial imaging during treatment. ARIAs were observed in 41% of patients during clinical studies. ARIAs may manifest as symptoms of headache, confusion, dizziness, vision changes, or nausea. Hypersensitivity reactions such as angioedema and urticaria have also occurred. Headache, falls, diarrhea, and altered mental status were additional adverse reactions reported by at least 2% of patients during aducanumab clinical trials. Aducanumab aims to slow the progression of Alzheimer's disease; it does not address specific symptoms or halt or cure the disease process.

There has been much criticism of aducanumab's approval. In November 2020, an 11-member expert advisory committee voted 8 against and 1 for approval; 2 were uncertain. Members against approval felt that the study failed to prove amyloid as a causative agent in Alzheimer's disease, given the substantial evidence of clearance without showing meaningful clinical improvement (Dyer 2021). Three committee members resigned in protest after the drug's approval (Mahase 2021). The post hoc reanalysis of the drug trials not only was felt to cast uncertainty on the study's validity but also was done in collaboration with the FDA, potentially compromising the agency's objectivity (Alexander *et al.* 2021). The FDA asked the U.S. Department of Health and Human Services inspector general to investigate whether there was improper contact, and the results are pending (Dyer 2021). Additional criticisms of aducanumab include the following: the drug's cost ($56,000 annually) and its impact on Medicare and health care costs in general; the lack of racial and ethnic diversity among trial participants (76% were white, 10% were Asian, and 3% were Hispanic; there was no African American representation); the uncertainty of benefit versus the certainty of ARIA risk; the lack of guidance and evidence on when to end treatment; and, finally, the risk of shutting down other avenues of research.

Lecanemab

On January 6, 2023, the FDA granted accelerated approval of lecanemab, and traditional approval followed on July 6, 2023. Lecanemab is a humanized immunoglobulin g1 monoclonal antibody that targets soluble aggregated Ab, with activity across oligomers, protofibrils, and insoluble fibrils. When studied in a randomized double-blind clinical trial, it met the primary endpoint of significant clinical change on CDR-SB scores at 18 months. Secondary endpoints were also met: a change in amyloid burden on PET and significant clinical change on the Alzheimer's Disease Assessment Scale (ADAS-cog14), the Alzheimer's Disease Composite Score (ADCOMS), and the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL). Participants in the trial had been diagnosed with either mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease-related dementia. Participants showed evidence of amyloid burden on PET scan or CSF testing and ranged in age from 50 to 90 years. Although efforts were made to ensure a more ethnically diverse enrollment, Black persons were still underrepresented. The most common adverse events were infusion-related reactions (26.4%), followed by ARIA with hemorrhages (17.3%) and ARIA with edema or effusion (12.6%). ARIAs were less common among ApoE e2 and ApoE e3 carriers, and while more common with ApoE e4 carriers, were most frequent with ApoE e4 homozygotes (Swanson *et al.* 2021; van Dyck *et al.* 2023).

Lecanemab is administered via a diluted intravenous infusion of 10 mg/kg over approximately 1 hour, once every 2 weeks (Esai Inc. 2023). A baseline MRI must be obtained prior to the initial treatment and prior to the 5th, 7th, and 14th infusions. If a patient reports symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI if indicated. If radiographically observed ARIA is confirmed, treatment recommendations are based on the type and severity of patient-experienced symptoms.

Criticisms of lecanemab include ongoing concerns regarding ARIA risks. While the majority of cases during the trial were asymptomatic, long-term effects have yet to be determined, and safety for individuals taking blood-thinning agents has yet to be established. There is also the questionably meaningful primary endpoint of a 0.45-point change on the CDR-SB, an 18-point scale. Health professionals express concerns that the drug will promote false hopes for significant improvements among those living with impairments. Cost also remains a concern. Many health care systems lack the infrastructure needed to administer lecanemab (i.e., staffing, PET imaging, and infusion centers). Medicare did commit to coverage following the FDA's traditional approval, contingent upon diagnosis with documented evidence of amyloid burden and physician enrollment in a Medicare-run registry. Manufacturers have listed an annual drug cost of $26,500, an expense that will impact the U.S. health care system and be unaffordable for lower-income countries, where the number of dementia cases is on the rise (Ferri and Jacob 2017; The Lancet 2022).

Cholinesterase-Related Therapies

In neurocognitive disorders, there are multiple physiological processes that destroy acetylcholine (acetylcholinesterase)-producing cells that in turn reduce cholinergic transmission in the brain (Bartus *et al.* 1982; Breijyeh and Karaman 2020; Tabet 2006). Acetylcholine is involved in processes such as memory, attention, sensory information, learning, and other critical functions. Because of acetylcholine's essential role in brain function, the cholinergic hypothesis arose in the 1970s as a contributing factor in the development of Alzheimer's disease (Bartus 2000; Breijyeh and Karaman 2020).

Acetylcholinesterase inhibitors increase acetylcholine by blocking the enzymes catalyzing its breakdown--that is, acetylcholinesterase and butyrylcholinesterase. These inhibitors can be classified as reversible, irreversible, and pseudo-reversible based on the degree of enzyme inhibition (Breijyeh and Karaman 2020; Giacobini 1998; Marucci *et al.* 2021).

Tacrine was the first acetylcholinesterase inhibitor (of both acetylcholinesterase and butyrylcholinesterase) and was approved by the FDA for Alzheimer's disease treatment in 1993. However, tacrine was discontinued in 2013 because of its significant side-effect profile, including hepatotoxicity. Donepezil, rivastigmine, and galantamine are the remaining FDA-approved acetylcholinesterase inhibitors that continue to be marketed and used to treat Alzheimer's disease (Sharma 2019). Efficacy for treatment of Alzheimer's disease is similar among acetylcholinesterase inhibitors (Arvanitakis *et al.* 2019; Birks 2006; Colovic *et al.* 2013; Seltzer 2006; Thompson *et al.* 2004).

Rivastigmine is additionally FDA approved to treat Parkinson's-related dementia. Acetylcholinesterase inhibitors are used to treat major neurocognitive disorder with Lewy bodies but are not FDA approved for this indication, so this use is considered off-label. Studies have shown statistically significant benefit but with associated adverse effects, specifically with rivastigmine and donepezil. Data for galantamine are limited (Stinton *et al.* 2015).

Acetylcholinesterase inhibitors are not FDA approved for mild neurocognitive disorders because studies have failed to show significant benefit for this condition (Arvanitakis *et al.* 2019; Cooper *et al.* 2013). Furthermore, these medications have not been approved or shown benefit for neurocognitive disorders that do not involve a

cholinergic deficit, such as frontotemporal variants, prion disease, Huntington's disease, and HIV infection.

These medications are only modestly effective in treating symptoms and do not prevent or cure neurodegenerative processes (Breijyeh and Karaman 2020). In a meta-analysis examining 80 trials of multiple acetylcholinesterase inhibitors in various forms of neurocognitive disorders, Mini-Mental State Examination results at 3, 6, and 12 months of treatment showed effect sizes of 1.08, 1.0, and 1.10 points, respectively (Knight *et al.* 2018). Research has been inconsistent in establishing preservation or improvement in functional capacity (activities of daily living) or management of adverse behaviors, but multiple studies have shown a reduced risk of nursing home placement associated with long-term acetylcholinesterase inhibitor use, specifically in Alzheimer's disease (Geldmacher *et al.* 2003; Knopman *et al.* 1996; Lopez *et al.* 2002).

The major side effects of acetylcholinesterase inhibitors are gastrointestinal, likely owing to acetylcholine being a primary gastrointestinal motility-enhancing transmitter, and occur in about 5% of users. Studies have also shown an associated risk of bradycardia (Isik *et al.* 2018), and there are case reports of an associated risk of QT interval prolongation and torsades de pointes (Malone and Hancox 2020).

Summary of Recommendations

Donepezil, rivastigmine, and galantamine are available for use orally (in tablet or capsule form, and/or as a oral solution), with a slow titration schedule over 4-8 weeks recommended for all three to minimize adverse effects, especially gastrointestinal distress. Side effects may abate at lower doses. Rivastigmine and donepezil are also available in a transdermal formulation, and donepezil additionally as an orally disintegrating tablet, allowing an alternate route when there are barriers to or difficulties with the usual routes of oral administration. In the moderate stage of a neurocognitive disorder, each acetylcholinesterase inhibitor may be used in combination with another FDA-approved pharmacological treatment, memantine. There is no clear evidence on the optimal duration of treatment with these medications (Marucci *et al.* 2021).

Donepezil

As a piperidine-based, reversible, noncompetitive acetylcholinesterase inhibitor with a plasma half-life of about 70 hours, donepezil was approved in the United States for the treatment of mild to moderate Alzheimer's disease in 1996 and for severe Alzheimer's disease in 2006. Donepezil is given once daily in a dose of 5, 10, or 23 mg. The 5-mg dose is only slightly less effective than the 10-mg dose and is an appropriate regimen for mild to moderate Alzheimer's disease, especially when tolerability is an issue (Birks and Harvey 2018). For moderate to severe Alzheimer's disease, 10-or 23-mg therapy is indicated; the 23-mg dose is generally initiated after a patient's disease has been stable for at least 3 months with the 10-mg dose. A 2018 Cochrane Review showed that benefits obtained with the 23-mg dose were no greater than those with the 10-mg dose, and the benefits of the 10-mg dose were only marginally better than those with the 5-mg dose (Birks and Harvey 2018). An extended-release capsule formulation containing both memantine and donepezil (Namzaric) has been available since 2014 for moderate to severe Alzheimer's disease.

Rivastigmine

Rivastigmine, a carbamyl derivative, is a slowly reversible inhibitor of acetylcholinesterase and butyrylcholinesterase with an elimination half-life of approximately 2 hours. It was approved in 2000 for use in the

United States and was indicated for the treatment of mild to moderate dementia of Alzheimer's and Parkinson's disease. In 2007, a rivastigmine 24-hour topical patch in dosages of 4.6, 9.5, and 13.3 mg/24 hours became the first transdermal patch to receive FDA approval for the treatment of mild to moderate Alzheimer's disease. In 2013, the FDA extended its approval for the higher dosage form (the 13.3-mg/24-hour dosage transdermal system) to include treatment of severe Alzheimer's disease. A 2015 Cochrane Review confirmed rivastigmine's benefit in the treatment of mild to moderate Alzheimer's disease but did not review the higher-dosage patch for severe stages of disease (Birks and Grimley Evans 2015). Rivastigmine inhibits the G1 isoenzyme of acetylcholinesterase selectively up to four times more potently than it does the G4 isoenzyme (Enz *et al.* 1993). This unique compound, with its butyrylcholinesterase inhibition properties, has been postulated to be of greater benefit than other acetylcholinesterase inhibitors in the treatment of Alzheimer's disease because butyrylcholinesterase activity increases in the hippocampus and cortex, whereas acetylcholinesterase activity diminishes (Tasker *et al.* 2005). To date, this effect has not been conclusively shown to be of clinical significance (Noetzli and Eap 2013). However, as a treatment involving multiple target receptor sites, this agent does have a theoretical advantage over single-target approaches. Rivastigmine capsules are available in doses of 1.5, 3, 4.5, and 6 mg, and the 24-hour transdermal patch is available in dosages of 4.6, 9.5, and 13.3 mg/24 hour. Transdermal administration and patches delivering a lower dosage compared with the pill form result in reduced side effects (especially gastrointestinal). A previously available rivastigmine oral solution product is not currently marketed in the United States.

For Alzheimer's disease, rivastigmine is initiated at 1.5 mg bid, taken orally. If tolerated, the dosage is increased every 2 weeks, first to 3 mg bid and then to 4.5 mg bid, up to a maximum dosage of 6 mg bid. Transdermal therapy is initiated at one 4.6-mg patch applied daily for at least 4 weeks, at which time the dosage may be increased to the 9.5-mg daily patch. Dosage may be further increased to 13.3 mg for severe stages of Alzheimer's disease. For Parkinson's disease, the oral rivastigmine dosage is increased as described for Alzheimer's disease, except that the minimum interval is extended to every 4 weeks (rather than every 2 weeks), up to a maximum dosage of 6 mg bid.

Galantamine

Galantamine hydrobromide (a tertiary alkaloid) is a specific, competitive, and reversible acetylcholinesterase inhibitor with a plasma half-life of 6-8 hours that was first marketed in the United States in 2001 as a treatment for mild to moderate dementia of Alzheimer's disease. Galantamine is unique in that it modulates neuronal nicotinic receptors (Coyle and Kershaw 2001). Whether this nicotinic receptor modulation imparts any significant clinical benefit in disease modification remains unknown. Oral dosing with galantamine tablets is initiated at 4 mg bid, with an increase after a minimum of 4 weeks to 8 mg bid as tolerated. The optimal dosage range is 16-24 mg/day. The extended-release galantamine capsule formulation for once-daily dosing has efficacy and side effects similar to that of the twice-daily dosing formulation; it is generally initiated at a dosage of 8 mg/day (taken in the morning), increased to 16 mg/day after a minimum interval of 4 weeks, and (if well tolerated after a minimum of 4 additional weeks) then increased to 24 mg/day. An oral solution (4 mg/mL) is available as well. Pooled data from early trials in patients with mild impairment showed significantly higher rates of death attributable to bronchial carcinoma, cerebrovascular disorder/syncope, myocardial infarction, and suicide in the galantamine-treated groups (Cusi *et al.* 2007; Loy and Schnieder 2006), although the use of cholinesterase inhibitors, including galantamine, reduced the risk of myocardial infarction and death in a different study (Nordstrom *et al.* 2013). Multiple studies of galantamine administered alone, with antipsychotic medication, with memantine, and a combination of all three have shown promise in the treatment of patients with schizophrenia (Koola 2016, 2018; Koola *et al.* 2014, 2020; Lee *et al.* 2007).

N-Methyl-D-Aspartate-Related Therapies

Glutamate is an agonist of kainite, *N*-methyl-D-aspartate (NMDA), and amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors. Neuronal plasticity of memory and learning is influenced by glutamate's direct modulation of the NMDA postsynaptic receptor. Glutamate acts as an excitatory neurotransmitter activating the NMDA receptor. Glutamate excess results in neurotoxicity, affecting cognitive functioning (Koch *et al.* 2005).

Summary of Recommendations

Memantine has been shown to reduce the level of cognitive impairment in patients with moderate to severe Alzheimer's disease (Bullock 2006; Nakamura *et al.* 2014; Reisberg *et al.* 2003). Initiation may be considered especially when acetylcholinesterase inhibitors have not been tolerated. Memantine in combination with an acetylcholinesterase inhibitor is an appropriate consideration for improvement in cognition and behavior. There is limited to poor evidence for memantine as a treatment for other neurocognitive disorders (McShane *et al.* 2019).

Memantine

Memantine is a noncompetitive NMDA receptor antagonist approved in the United States for the treatment of moderate to severe Alzheimer's disease. The NMDA receptor modulates memory function. Memantine's low-affinity antagonism of glutamate, which has been linked to neurodegeneration and excitotoxicity, may protect against neurotoxicity (Lipton and Rosenberg 1994).

Memantine is available in tablets, in extended-release capsules, and as an oral solution. It is recommended that memantine tablets be initiated at a dosage of 5 mg/day for 1 week and increased weekly by 5 mg/day up to a target dosage of 20 mg/day. Memantine tablets are generally given in twice-daily doses, although the elimination half-life ranges from 60 to 80 hours. Memantine is also available in a once-daily extended-release capsule formulation (7, 14, 21, and 28 mg); it is recommended that memantine capsules be initiated at a dosage of 7 mg/day for 1 week, increasing by 7 mg/day after a minimum of 1 week to 14 mg/day, up to a target dosage of 28 mg/day. Memantine

dosing should be adjusted for patients with moderate to severe renal impairment, with a target of 14 mg/day. The most common adverse effects are drowsiness, dizziness, confusion, headache, and constipation.

Memantine Combination Therapy

Memantine in combination with an acetylcholinesterase inhibitor has been shown to improve cognitive domains and to ameliorate symptoms of behavioral dyscontrol (agitation/aggression, eating/appetite, irritability/lability) (Cummings *et al.* 2006; Schmidt *et al.* 2015; Tariot *et al.* 2004). Given the disruption of multiple neurotransmitter systems and pathways in neurocognitive disorders, the use of adjunctive cognition-enhancing medications is understandable (Grossberg *et al.* 2006; Koola *et al.* 2014). The specific neurobiological deficits that may be affected by a pharmacological or nutraceutical intervention should be considered. In 2014, fixed-dosage combinations of extended-release memantine (14 or 28 mg) and donepezil (10 mg) became available. Patients without severe renal impairment who are currently taking donepezil 10 mg/day and extended-release memantine 10 mg bid or 28 mg once daily may be switched to the memantine 28 mg/donepezil 10 mg combination tablet, which can be taken once daily.

Vascular and Inflammation-Related Therapies

Major known modifiable risk factors for cognitive impairment (with or without dementia) include diabetes mellitus, hypertension, cardiac ischemia, atrial fibrillation, smoking, hyperlipidemia, and peripheral vascular disease (Desmond *et al.* 1993; Rockwood *et al.* 1997). Controversial risk factors include hyperhomocysteinemia. Established vascular therapeutic interventions have included low-dose aspirin and other antiplatelet agents, anticoagulants, antihypertensives, aggressive management of diabetes, carotid endarterectomy for selected patients, and treatment of hyperlipidemia. There is a significant overlap of patients with vascular cognitive impairment and those with Alzheimer's disease (Gearing *et al.* 1995; O'Brien 1994). Cholinergic receptors (muscarinic and nicotinic) are known modulators of cerebral blood flow (Schwarz *et al.* 1999; Zhang *et al.* 1998). However, the notion of overlap has been challenged by evidence that the cholinergic system may be intact in individuals with "pure" vascular dementia but be compromised to the same extent as in Alzheimer's disease in individuals with a mixed etiology of both Alzheimer's and vascular disease (O'Brien and Thomas 2015). Currently, a large burden of vascular disease pathology (large-vessel to microvascular disease and focal, multifocal, or diffuse lesions) in the absence of other neurodegenerative processes, as well as a clear relation of the cognitive decline or progression to the lesions, is needed to make a diagnosis of a vascular neurocognitive disorder. Vascular pathology should otherwise be considered as contributory to impairment and not the primary cause (O'Brien and Thomas 2015).

The effectiveness of acetylcholinesterase inhibitors and memantine in treating vascular dementia has been insufficient to support these agents' widespread use. There is currently no FDA-approved treatment for vascular dementia. A 2021 Cochrane Review specifically examined acetylcholinesterase inhibitors, with three trials studying donepezil, three studying rivastigmine, and two studying galantamine. There was moderate to high certainty of evidence for a slight effect on cognition for donepezil

and galantamine, but the size of the change was unlikely to register as clinically beneficial. The evidence for rivastigmine was less certain and was determined to need more research, especially regarding the transdermal form (Battle *et al.* 2021).

There is limited evidence that managing vascular risk factors lowers the risk for vascular cognitive impairment. There have been mixed results in studies on blood pressure and glycemic and cholesterol control. The use of aspirin, other nonsteroidal anti-inflammatory drugs, or statins to prevent and treat vascular dementia is currently not well supported by the literature (Iadecola *et al.* 2019; Jaturapatporn *et al.* 2012; McGuinness *et al.* 2016).

Other Therapies

Antioxidant-related treatment for cognitive impairment remains poorly supported by placebo-controlled, double-blind studies. *Ginkgo biloba* could be classified within several potential treatment categories, including antioxidants, nutraceuticals, cholinergic agents, and vasodilators; most studies have shown no to only marginal benefit for this agent (Laws *et al.* 2012). Vitamin E (including tocopherols and tocotrienols), vitamin C, and carotenoids have antioxidant properties; however, reports of benefit in treating patients with cognitive impairment are mixed. Although antioxidants may have potential as a combination therapy modality, further research is required before endorsing specific treatment recommendations with current antioxidants.

Various other agents are being tested and studied for their potential to improve cognitive impairment. Examples include anti-tau therapies (most are immunotherapies, but only an aggregation inhibitor has reached Phase III status), tramiprosate, modafinil, hormone replacement therapy, nutraceuticals (e.g., *Rubia cordifolia*, *Salvia lavandulaefolia*, *Rosmarinus officinalis*, *Melissa officinalis*), dehydro-3-epiandrosterone, aniracetam, piracetam, latrepirdine, and unifiram. Currently, no recommendations can be made for use of any of these agents as monotherapy or combination therapy.

Conclusion

The molecular pathogenesis of nerve cell death remains elusive, especially as it relates to the onset and progression of cognitive impairment. Alzheimer's disease and other types of cognitive impairment represent a wide spectrum of neurosystem dysfunction, and no single treatment modality yet found is sufficient to address the global apoptosis and degeneration that occur. Combination therapies (pharmacodynamically exerting multiple effects on disease pathology) have proven successful in the treatment of cancer and HIV infection. The same synergistic approach to treating neurocognitive disorders may be required (Campos *et al.* 2016; Cummings *et al.* 2019; Salloway *et al.* 2020; Tomaszewski *et al.* 2016).

As it has become clearer that neurodegeneration often precedes the manifestation of cognitive deficits, accurate assessment of individual genetic risk followed by routine approved biomarkers may lead to very targeted, disease-altering treatment even in the prodromal stage of the disease (Ghosh *et al.* 2020).

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CHAPTER 44

Sedative-Hypnotics

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In this chapter we examine some of the pharmacological properties of benzodiazepines, barbiturates, and other sedative-hypnotic compounds, including orexin (hypocretin) receptor antagonists and melatonin receptor agonists (Figure 44-1). Sedative drugs moderate excitement, decrease activity, and induce calmness, whereas hypnotic drugs produce drowsiness and facilitate the onset and maintenance of a state that resembles normal sleep in its electroencephalographic characteristics. Although these agents are CNS depressants, they usually produce therapeutic effects at dosages much lower than those that cause coma and generalized depression of the CNS.

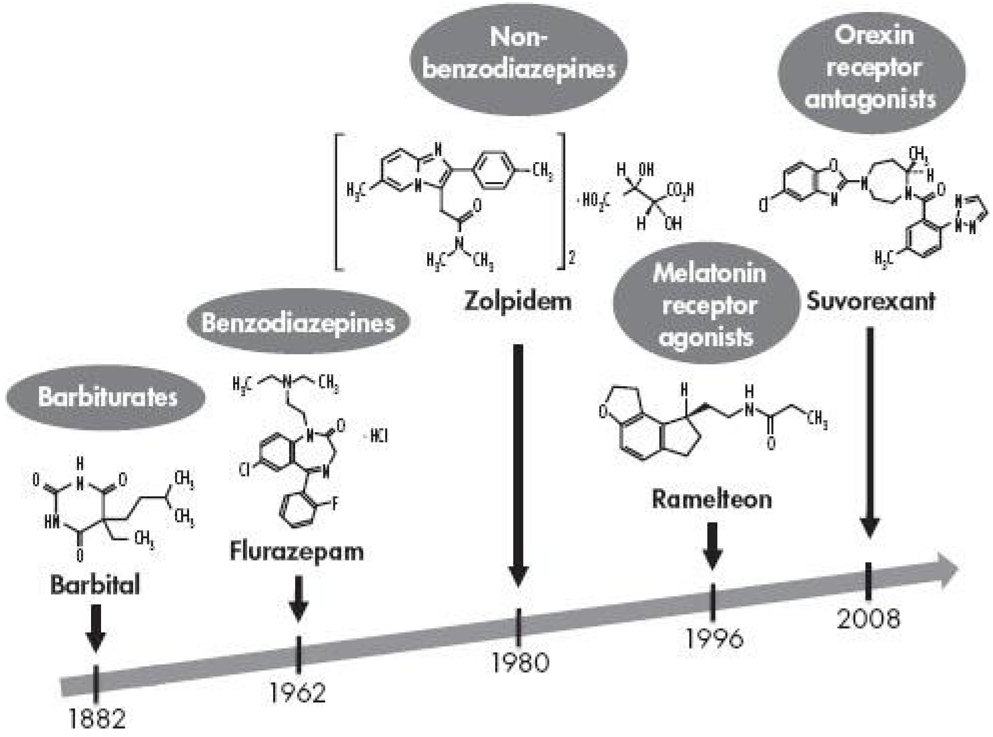
Non-benzodiazepines
Orexin receptor antagonists
Zolpidem
Melatonin receptor agonists
Suvorexant
Benzodiazepines
Barbiturates
Flurazepam
Ramelteon
Barbital
1882
1962
1980
1996
2008

FIGURE 44-1. History of sedative-hypnotic development.

Some sedative-hypnotic drugs have other therapeutic uses as muscle relaxants (especially benzodiazepines), antiepileptics, or preanesthetic medications. Although benzodiazepines are used widely as antianxiety drugs, it is not known whether their effect on anxiety is truly distinct from their sleep-inducing effect.

Sedative-hypnotics are also important drugs to neuroscientists. These substances modulate basic behaviors such as arousal and response to stress. Through our increasing understanding of the molecular structure of the GABA type A ($GABA_A$) receptor, the cellular mechanisms of these compounds' modes of action have been elucidated.

In 2000, it was discovered that human narcolepsy-cataplexy was associated with deficiency of a newly discovered neuropeptide, orexin (or hypocretin) (Nishino *et al.* 2000). Although replacement therapies for the orexin-deficient narcolepsy using synthetic small-molecule orexin receptor agonists are not yet available, dual orexin receptor antagonists have been developed and were approved by the FDA in 2014 for the treatment of insomnia.

Further understanding of their mode of action could thus help to elucidate neurochemical and neurophysiological control of sleep and sleep-related physiology and behaviors.

Benzodiazepines and Benzodiazepine-Like Agents

History and Discovery

Benzodiazepines were first synthesized in the 1930s. The introduction of chlorpromazine and meprobamate in the early 1950s led to a decade of development of sophisticated in vivo pharmacological screening methods that were used to identify the sedative properties of benzodiazepines. More than 3,000 benzodiazepines have been synthesized since chlordiazepoxide (synthesized by Sternbach in 1957; see Baenninger 2004) was introduced into clinical medicine. About 40 of them are in clinical use.

Several drugs chemically unrelated to the benzodiazepines have been shown to exhibit sedative-hypnotic effects with a benzodiazepine-like profile, and these drugs have been found to act via the benzodiazepine binding site on the $GABA_A$ receptor (see "Molecular Mechanism of $GABA_A$-Benzodiazepine Receptor Interaction" section later in this chapter).

Most benzodiazepines currently on the market were selected for their high anxiolytic potential rather than their CNS depressant effects. Nevertheless, all benzodiazepines

have sedative-hypnotic properties to various degrees, and some compounds that facilitate sleep have been used as hypnotics.

Mainly because of their remarkably low capacity to produce fatal CNS depression, benzodiazepines have displaced barbiturates as the preferred sedative-hypnotic agents.

Structure-Activity Relations

The term *benzodiazepine* refers to the portion of the structure composed of benzene rings (*A* in the top portion of Figure 44-2) fused to a seven-membered diazepine ring (*B*). However, most of the older benzodiazepines contain a 5-aryl substituent *(C)* and a 1,4-diazepine ring, and the term has come to mean the 1,4-benzodiazepines.

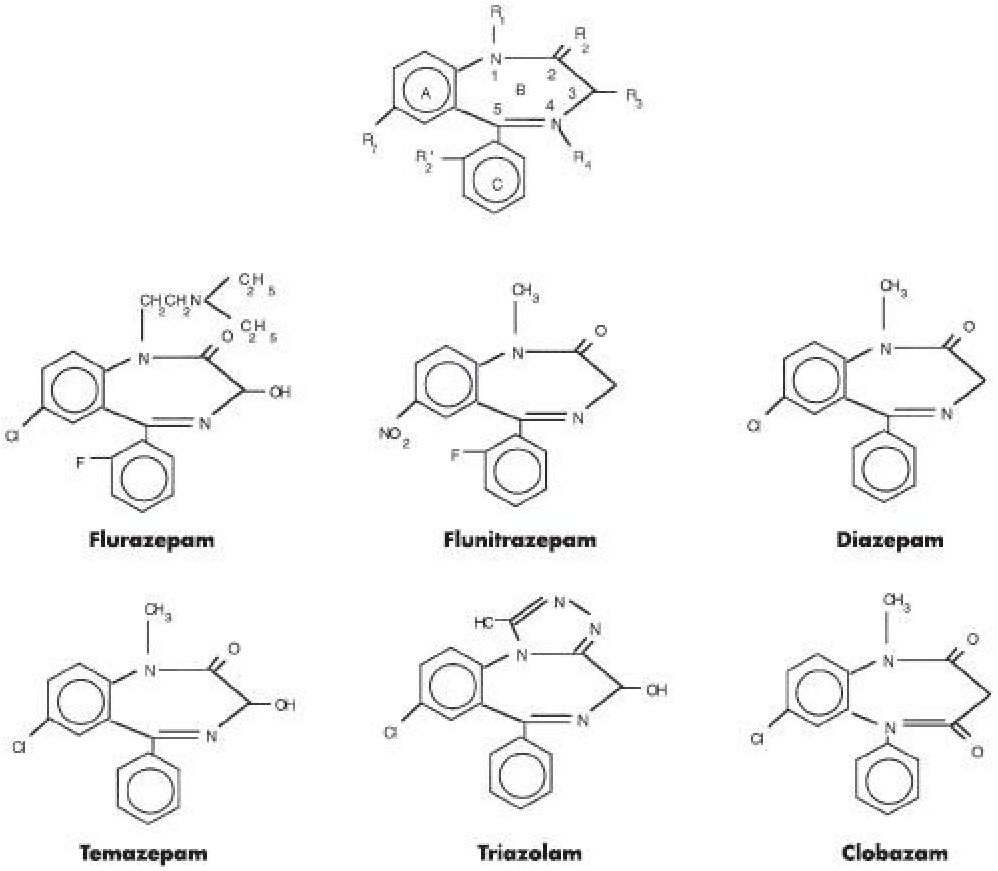

FIGURE 44-2. Chemical structures of some commonly used benzodiazepines.

The term *benzodiazepine* refers to the portion of the structure composed of benzene rings (*A* in the top portion of figure) fused to a seven-membered diazepine ring (*B*). However, most of the older benzodiazepines contain a 5-aryl substituent *(C)* and a 1,4-diazepine ring, and the term has come to mean the 1,4-benzodiazepines.

A substituent (most often chloride) at position 7 is essential for biological activity. A carbonyl at position 2 enhances activity and is generally present. Most of the newest products, such as flurazepam, also substitute the 2 position. These general features are important for the metabolic fate of the compounds. Because the 7 and 2 positions of the molecule are resistant to all major degradative pathways, many of the metabolites retain substantial pharmacological activity.

Pharmacological Profile

Benzodiazepines share anticonvulsant and sedative-hypnotic effects with the barbiturates. In addition, they have a remarkable ability to reduce anxiety and aggression (Cook and Sepinwall 1975). In the mammalian CNS, two subtypes of benzodiazepine omega (o) receptors have been pharmacologically recognized. Benzodiazepine o_1 receptors are sensitive to b-carbolines, imidazopyridines (e.g., zolpidem), and triazolopyridazines. Benzodiazepine o_2 receptors have low affinity for these ligands but high affinity for benzodiazepines. Benzodiazepine o_1 sites are enriched in the cerebellum, whereas o_2 sites are present mostly in the spinal cord, and both receptor subtypes are found in the cerebral cortex and hippocampus. Benzodiazepine o_1 and o_2 receptor subtypes are also located peripherally in adrenal chromaffin cells.

Another benzodiazepine subtype, o_3, was identified and is commonly called the peripheral benzodiazepine receptor subtype because of its distribution on glial cell membranes in nonnervous tissues such as adrenal, testicular, liver, heart, and kidney. This subtype was later detected in the CNS, especially on the mitochondrial membrane, and not in association with GABA$_A$ receptors (Gavish *et al.* 1992). The o_3 receptor subtype has high affinity for benzodiazepines and isoquinoline carboxamides (Awad and Gavish 1987). The functional role of this receptor subtype is unknown, but it may be involved in the biosynthesis and mediation of the sedative-hypnotic effects of certain neuroactive steroids (e.g., pregnenolone, dehydroepiandrosterone, allopregnanolone, tetrahydrodeoxycorticosterone) (Edgar *et al.* 1997; Friess *et al.* 1996; Rupprecht *et al.* 1996). Neurosteroids modulate GABA$_A$-mediated transmission through an allosteric mechanism that is distinct from the modulation mechanism of benzodiazepines and barbiturates. Through stimulation of o_3 receptors with agonists, cholesterol is transferred from intracellular stores in mitochondria and becomes available to the mitochondrial cytochrome P450 (CYP) cholesterol side chain cleavage enzyme, and neurosteroid biosynthesis begins (Papadopoulos *et al.* 2001). Benzodiazepine o_3 receptor subtypes also may serve as mitochondrial membrane stabilizers and protect against pathologically induced mitochondrial and cell toxicity (Papadopoulos *et al.* 2001).

The $GABA_A$ receptor is a ligand-gated ion channel that mediates fast synaptic neurotransmission in the CNS. When the $GABA_A$ receptor is occupied by GABA or GABA agonists such as muscimol, the chloride channels open and chloride ions diffuse into the cell. Early research established that diazepam (and related benzodiazepines) does not act directly through GABA but instead modulates inhibitory transmission through the $GABA_A$ receptor in some other way. It was subsequently discovered that benzodiazepines bind specifically to neural elements in the mammalian brain with high affinity and that an excellent correlation exists between drug affinities for these specific binding sites and in vivo pharmacological potencies (Mohler and Okada 1977; Squires and Brastrup 1977).

The binding of a benzodiazepine to the $GABA_A$ receptor site is enhanced in the presence of GABA or a GABA agonist, suggesting that a functional (but independent) relationship exists between the $GABA_A$ receptor and the benzodiazepine receptor binding sites (Tallman *et al.* 1978). Barbiturates (and to some extent alcohol) also seem to produce anxiolytic and sedative effects at least partly by facilitating GABAergic transmission (see "Barbiturates" section later in this chapter). This common action for chemically unrelated compounds can be explained by the shared ability of these compounds to stimulate specific sites on the $GABA_A$ receptor.

The benzodiazepines bind with high affinity to their binding sites so that the action of GABA at its receptor site is allosterically enhanced. GABA can produce stronger postsynaptic inhibition in the presence of a benzodiazepine. Benzodiazepine agonists are assumed to potentiate only ongoing physiologically initiated actions of GABA (at $GABA_A$ receptors), whereas barbiturates are thought to cause inhibition at all GABAergic synapses regardless of their physiological activity. In addition, barbiturates appear to increase the duration of the open state of the chloride channel, whereas benzodiazepines increase the frequency of channel openings but have little effect on duration (Twyman *et al.* 1989). These fundamental differences between the allosteric effects of benzodiazepines within the $GABA_A$ receptor and the conducive effects of barbiturates on the chloride ion channel may explain why low dosages of barbiturates have a pharmacological profile similar to that of benzodiazepines, whereas high dosages of barbiturates cause a profound and sometimes fatal suppression of brain synaptic transmission. It is notable that selective $GABA_A$ receptor agonists, such as muscimol, have no sedative or anxiolytic properties; thus, the entire $GABA_A$-benzodiazepine receptor complex must be involved for expression of sedative-hypnotic properties.

Molecular Mechanism of $GABA_A$-Benzodiazepine Receptor Interaction

The structure of the $GABA_A$-benzodiazepine receptor complex (Figure 44-3) was elucidated through the cloning of all of the implicated subunit genes and the study of the corresponding encoded proteins. The $GABA_A$ receptor is a pentameric protein consisting of five subunits that form a rosette surrounding a transmembrane ion channel pore for $Cl^{[?]}$ (see Figure 44-3A). The $GABA_A$ receptor in humans includes the following known subunits: a_1-a_6, b_1-b_4, g_1-g_4, d, e, p, and t (seven kinds of subunits, 18 isoforms total) (Mehta and Ticku 1999). Two alternatively spliced versions of the g_2 subunit, g_{2S} and g_{2L}, are also known to exist (Kofuji *et al.* 1991).

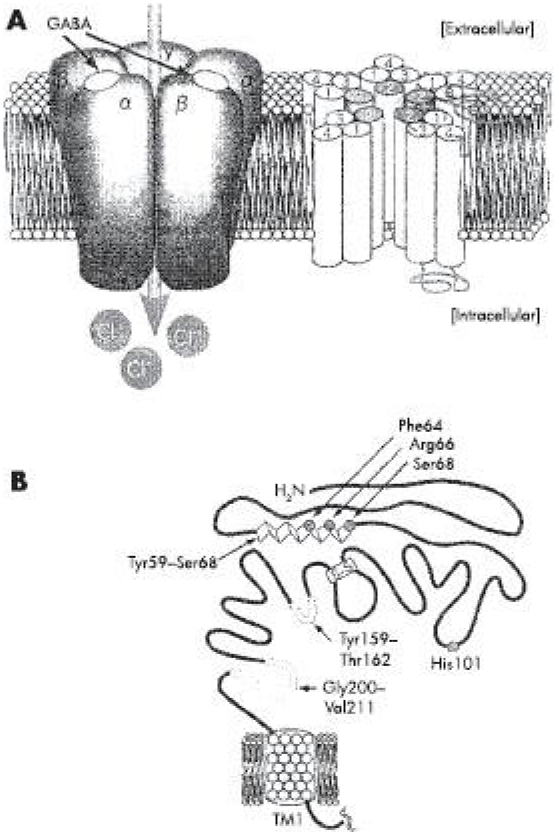

FIGURE 44-3. GABA$_A$-benzodiazepine receptor complex.

(A) Schematic model of the mammalian GABA$_A$ receptor embedded in the cell membrane, containing the a, b, and g subunits (in a ratio of 2:2:1). The binding of two molecules of GABA *(arrows)* to the action site (composed of a and b subunits) triggers the opening of the chloride channel pore, causing chloride ions (Cl$^{[?]}$) to diffuse into the cell. Each a or b subunit is composed of four transmembrane (TM) regions (TM1-TM4). The ion channel central pore is lined by TM2 regions contributed by five subunits, arranged in a rosette formation. **(B)** Structure of the a$_1$ subunit, with amino acid sequence, indicating amino acid residues implicated in GABA and benzodiazepine binding domains.

Source. Modified from Ueno *et al.* 2001.

Despite many studies, the physiological and neuroanatomic processes mediating benzodiazepine action on the GABA$_A$ receptor complex remain poorly understood. One reason is that the GABAergic system is the most widespread of all inhibitory neurotransmitter systems and could be involved in many circuits responsive to various effects of benzodiazepine agonists. In addition, the various GABA$_A$ receptor subtypes have different ligand affinities and channel functions in response to benzodiazepine agonists. These GABA$_A$ receptor subtypes are broadly distributed in various brain areas to form a mosaic of receptor subtypes (Wisden and Stephens 1999), making it difficult to understand the functional mechanisms of interaction of benzodiazepine agonists with the GABA$_A$-ergic system from the physiological point of view (Rudolph *et al.* 1999). However, site-directed mutagenesis and gene knock-in techniques have identified several important features of the benzodiazepine action sites on GABA$_A$ receptors and their physiological functions (Ueno *et al.* 2001).

It is postulated that the binding of GABA to *N*-terminal extracellular domains of a and b subunits causes conformational changes within the subunits. Ion channel pores subsequently open, and Cl$^{[?]}$ flows across the neuronal membrane, resulting in neuronal inhibition (Amin and Weiss 1993; Boileau *et al.* 1999; Sigel *et al.* 1992; Smith and Olsen 1994) (see Figure 44-3A). The extracellular domains of the a and g subunits, which consist of about 220 amino acids in the *N*-terminal region, also have been shown to bind GABA and benzodiazepines. "Pharmacologically classified" o$_1$ and o$_2$ receptors are now thought to correspond to GABA$_A$ receptors possessing the a$_1$ and a$_2$ subunits and the a$_3$ and a$_5$ subunits, respectively.

Extracellular benzodiazepine binding sites on these subunits consist of several divided portions (see Figure 44-3B). His101, Tyr159-Thr162, and Gly200-Val211 on a$_1$ subunits, as well as Lys41-Trp82 and Arg114-Asp161 on g$_2$ subunits, are essential to formation of the binding pockets (Boileau *et al.* 1998). Most strikingly, His101 is a critical residue for diazepam to exert its sedative effect (Crestani *et al.* 2001; Low *et al.* 2000; McKernan *et al.* 2000; Rudolph *et al.* 1999). Knock-in mice with displacement of His101Arg are insensitive to benzodiazepine-induced allosteric modulation of the complex but have preserved physiological regulation by GABA

(Rudolph *et al.* 1999). These knock-in mice were not sedated by diazepam but retained other effects of diazepam, such as the drug's anxiolytic-like, myorelaxant, motor-impairing, and ethanol-potentiating effects. This finding suggests the possibility that the sedative action of the benzodiazepine is mediated through $GABA_A$ receptors possessing the a_1 subunit. It is also noteworthy that the His101Arg knock-in mice responded to diazepam and showed sleep changes similar to those seen in wild-type mice, despite the lack of sedative response in these animals (Tobler *et al.* 2001). Thus, the hypnotic and sedative effects of benzodiazepines may be mediated via different subtypes, with hypnotic effects involving $GABA_A$ receptors possessing subunits other than a_1 (i.e., a_2, a_3, or a_5) (Tobler *et al.* 2001).

Nonbenzodiazepine Hypnotics (Acting on the Benzodiazepine Receptor)

Until about 1980, it was widely accepted that the benzodiazepine structure was a prerequisite for the compound's anxiolytic profile and for benzodiazepine receptor recognition and binding. However, more recently, three chemically unrelated drugs--the imidazopyridine zolpidem, the cyclopyrrolone zopiclone (which is not FDA approved, although its *S*[+]-enantiomer, eszopiclone, is FDA approved), and the pyrazolopyrimidine zaleplon--have been shown to be useful sedative-hypnotics with benzodiazepine-like profiles (Figure 44-4). Other chemical classes of drugs that are structurally dissimilar to the benzodiazepines (e.g., triazolopyridazines) but act through the benzodiazepine receptor also have been developed and have demonstrated anxiolytic activity in humans.

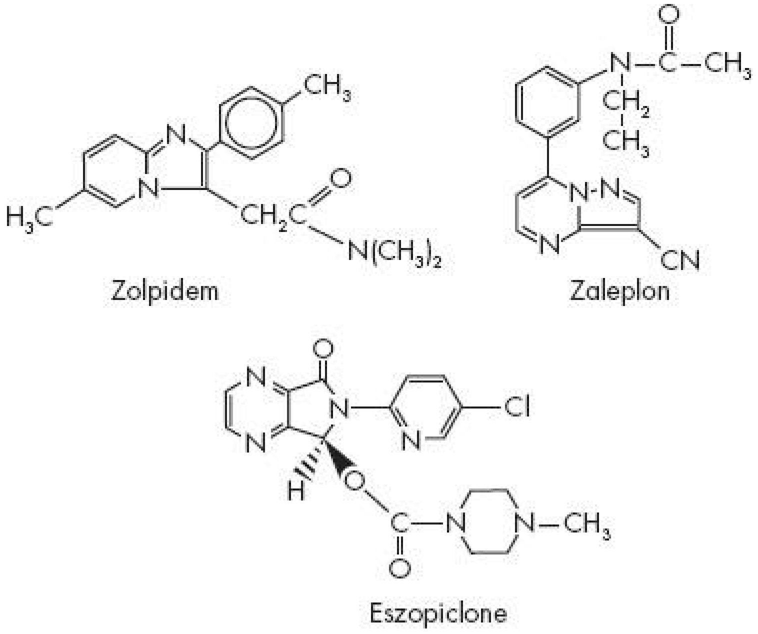

FIGURE 44-4. Nonbenzodiazepine hypnotics.

Three drugs chemically unrelated to the benzodiazepines--zolpidem (an imidazopyridine), eszopiclone (a cyclopyrrolone), and zaleplon (a pyrazolopyrimidine)--are useful sedative-hypnotics with benzodiazepine-like profiles.

Nonbenzodiazepine hypnotics have a pharmacological profile slightly different from that of classic benzodiazepines. For example, zolpidem binds selectively to o_1 (the 50% inhibitory concentration [IC_{50}] ratio for o_1/o_2 is nearly 1:10) and has more prominent sedative-hypnotic properties relative to other properties such as anxiolytic activity or muscle relaxation. Zolpidem and zopiclone have short half-lives (3 hours and 6 hours, respectively). These drugs appear not to appreciably affect the rapid eye movement (REM) sleep pattern, whereas the amount of slow-wave sleep (SWS) may be slightly increased (Jovanovic and Dreyfus 1983; Shlarf 1992). Rebound effects (insomnia, anxiety), which are commonly seen after withdrawal of short-acting benzodiazepines, are minimal for zolpidem and zopiclone. These compounds also induce little respiratory depression and have less abuse potential than do the common clinical benzodiazepine hypnotics. However, much longer clinical trials are needed to definitively determine whether the imidazopyridines or cyclopyrrolones have any significant advantages over the short-to medium-half-life benzodiazepines in the treatment of insomnia. Eszopiclone, the active stereoisomer of zopiclone with a longer half-life, was approved by the FDA in 2004 and is thought to be helpful in sleep maintenance as well as sleep induction. Because eszopiclone induces little tolerance, it is suitable for long-term use.

Zaleplon, a pyrazolopyrimidine, also has been developed as a novel nonbenzodiazepine hypnotic (see Figure 44-4). Clinical trials demonstrated that zaleplon is a well-tolerated, safe, rapidly acting, and effective sedative with advantages over lorazepam in regard to unwanted cognitive and psychomotor impairment (Allen *et al.* 1993; Beer *et al.* 1994).

Benzodiazepine Antagonists, Partial Agonists, and Inverse Agonists

As knowledge of the relation between the structure of benzodiazepine receptor ligands and their pharmacological properties has increased, potent receptor agonists that stimulate the receptor and produce pharmacological effects qualitatively similar to those of the classic benzodiazepines have been developed. Antagonists, which block the effects of the agonists without having any effects themselves, and partial agonists, which have a mixture of agonistic and antagonistic properties, also have been introduced (Haefley 1988). Development of partial agonists may be particularly important in the future because these compounds are free of the ataxic and amnesic side effects commonly associated with the classic benzodiazepine hypnotics.

Braestrup and Nielsen (1986) found that a group of nonbenzodiazepine compounds, the b-carbolines, not only antagonized the action of the full agonists but also had intrinsic activity themselves. These compounds are called benzodiazepine inverse agonists because they have biological effects exactly opposite those of the pure agonists while also having intrinsic activity like that of agonists. The effects of inverse agonists are blocked by antagonists; thus, the benzodiazepine receptor is unique in that it has a bidirectional function (Figure 44-5).

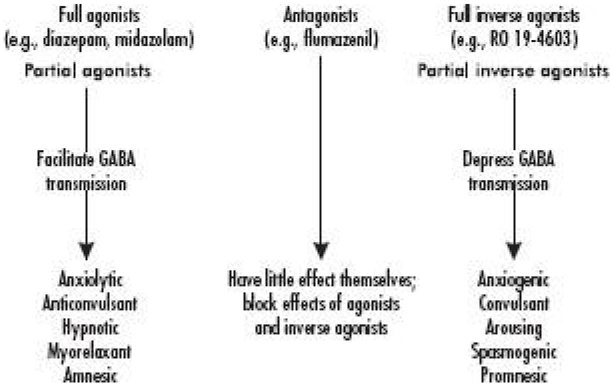
Full agonists
(e.g., diazepam, midazolam)
Partial agonists
Facilitate GABA transmission
Anxiolytic
Anticonvulsant
Hypnotic
Myorelaxant
Amnesic
Antagonists
(e.g., flumazenil)
Have little effect themselves; block effects of agonists and inverse agonists
Full inverse agonists
(e.g., RO 19-4603)
Partial inverse agonists
Depress GABA transmission
Anxiogenic
Convulsant
Arousing
Spasmogenic
Promnesic

FIGURE 44-5. Properties of the various types of benzodiazepine receptor ligands.

Natural Ligands for Benzodiazepine Receptors in the Brain

The presence of benzodiazepine receptors in the brain suggests that natural ligands modulate GABAergic transmission through these sites. Small amounts of endogenous

benzodiazepines (e.g., diazepam, desmethyldiazepam) can be detected in human and animal tissues. These benzodiazepines probably originate from plants, such as wheat, corn, potatoes, or rice, and the levels that are detected are too low to be pharmacologically active (e.g., diazepam, < 1 ng/g; desmethyldiazepam, 0.5 ng/g).

Other endogenous benzodiazepine-like substances with neuromodulatory effects probably exist in mammals. Endogenous ligands called diazepam binding inhibitors, or endozepines, that bind to the benzodiazepine site on the $GABA_A$-ergic receptor complex were identified and isolated (Costa and Guidotti 1991; Marquardt *et al.* 1986; Rothstein *et al.* 1992). Like benzodiazepines, these ligands potentiate $GABA_A$ receptor-mediated neurotransmission by acting as positive allosteric modulators (PAMs) of this receptor. Endozepines are present in the brain at pharmacologically active concentrations and may play a role both physiologically (e.g., regulation of memory, sleep, and learning) and pathologically (e.g., panic attacks, hepatic encephalopathy) (Mullen *et al.*

1990; Nutt *et al.* 1990). Finally, endozepines have been implicated in idiopathic recurring stupor, a neurological condition characterized by recurrent episodes of stupor or coma in the absence of any known toxic, metabolic, or structural brain damage (Cortelli *et al.* 2005). Endozepine concentrations are greatly elevated in the plasma of individuals with this condition, and stupor can be interrupted by injections of flumazenil, a benzodiazepine antagonist. Thus, the roles of endozepines in physiological and pathological processes should be elucidated once these endogenous ligands have been isolated and characterized (Farzampour *et al.* 2015; Rothstein *et al.* 1992).

Recently it was reported that activities of substances in cerebrospinal fluid (CSF) that augment inhibitory GABA signaling are enhanced in patients with hypersomnia (Rye *et al.* 2012). The authors demonstrated that in the presence of GABA, CSF can stimulate $GABA_A$ receptor function in vitro (measures of $GABA_A$ receptor-mediated chloride currents in recombinant pentameric human $GABA_A$ receptor-expressed cultured cells). Interestingly, stimulations of $GABA_A$ receptor function by CSF from patients with hypersomnolence (individuals with idiopathic hypersomnia with and without long sleep, long sleepers, and individuals with narcolepsy without cataplexy) were significantly enhanced in comparison to CSF from control subjects. This bioactive CSF component had a mass of 500-3,000 daltons and was neutralized by trypsin. Flumazenil, a benzodiazepine receptor antagonist, reversed enhancement of

$GABA_A$ signaling by hypersomnolent CSF in vitro, and also normalized vigilance in all seven hypersomnolent patients who underwent the drug challenge (Rye *et al.* 2012). The authors conclude that a naturally occurring substance in CSF augments inhibitory GABA signaling, revealing a new pathophysiology associated with hypersomnia; the results also suggest the existence of other endogenous $GABA_A$ receptor modulators in the CNS.

Pharmacokinetics and Disposition

Benzodiazepines

Benzodiazepines are generally absorbed rapidly and completely. Plasma binding is high (e.g., about 98% for diazepam).

Benzodiazepines are very lipophilic (except for oxazepam), and penetration into the brain is rapid. For swift onset of action, diazepam is available as an emulsion that is administered intravenously for rapid control of epilepsy; midazolam is a water-soluble benzodiazepine suitable for intravenous injection.

The major metabolic pathways for the 1,4-benzodiazepines are shown in Figure 44-6. Medazepam is metabolized to diazepam, which is *N*-desmethylated to desmethyldiazepam. Chlordiazepoxide is also partly converted to desmethyldiazepam. Clorazepate is transformed to desmethyldiazepam.

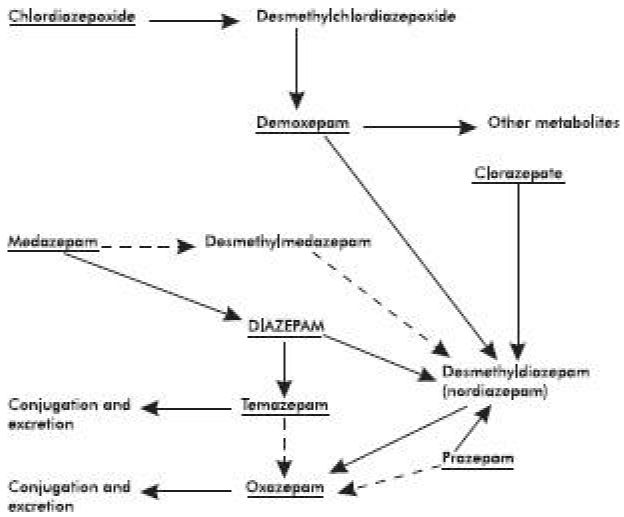
Chlordiazepoxide
Desmethylchlordiazepoxide
Demoxepam
Other metabolites
Clorazepate
Medazepam
Desmethylmedazepam
DIAZEPAM
Desmethyldiazepam (nordiazepam)
Conjugation and excretion
Temazepam
Prazepam
Conjugation and excretion
Oxazepam

FIGURE 44-6. Metabolic pathways for the principal 1,4-benzodiazepines.

Solid arrows and *broken arrows* denote major and minor pathways, respectively; commercially available drugs are underscored. Flurazepam, flunitrazepam, nitrazepam, and triazolam have separate metabolic pathways.

Desmethyldiazepam is a critical metabolite for biological activity because of its long half-life (> 72 hours). Because diazepam's half-life is about 36 hours, the concentration of its desmethyl derivative soon exceeds that of the parent drug during long-term administration. Desmethyldiazepam undergoes oxidation to oxazepam, which (like its 3-

hydroxy analog temazepam) is rapidly conjugated with glucuronic acid and excreted.

Among the various benzodiazepines, triazolam has a particularly short half-life (< 4 hours), and flurazepam and nitrazepam both have long half-lives. A major active metabolite of flurazepam, *N*-desalkylflurazepam, has a very long half-life (~ 100 hours).

Because benzodiazepines are often prescribed for long periods, their long-term pharmacokinetics are particularly important. Concentrations of diazepam and desmethyldiazepam reach a plateau after a few weeks. Diazepam concentrations may then decline somewhat, without much change in the concentration of the desmethyl metabolite.

Although benzodiazepines can stimulate liver metabolism in some animals, their induction of the hepatic microsomal enzyme system (CYP enzymes) is of little clinical significance in humans.

Nonbenzodiazepine Hypnotics

Regarding the pharmacokinetics of nonbenzodiazepine hypnotics, no (or only weak) active metabolites exist for the compounds currently available.

Effects on Stages of Sleep

The hypnotic effects of benzodiazepines are thought to derive from the inhibitory effects of the GABAergic system on the raphe and locus coeruleus monoaminergic ascending arousal systems, but this hypothesis may only partially explain their action. Magnocellular regions of the basal forebrain and the preoptic areas have been recognized as important sites for SWS regulation (Szymusiak 1995). Neurons that are selectively active during SWS have been described in these structures, most typically in the ventrolateral preoptic areas (Saper *et al.* 2001; Sherin *et al.* 1996). These neurons contain GABA and galanin, an inhibitory peptide, and project to the main components of the ascending arousal system, such as the raphe and locus coeruleus and brain stem cholinergic nuclei (Saper *et al.* 2001). The ventrolateral preoptic nucleus also sends a dense inhibitory projection to the tuberomammillary histaminergic nucleus, another important wake-promoting system (see Saper *et al.* 2001; Sherin *et al.* 1996). Benzodiazepines may thus indirectly modulate these wake-active monoaminergic neurons to promote their hypnotic effects.

Another important site of action for benzodiazepines may be the suprachiasmatic nucleus (SCN). In SCN-lesioned animals, benzodiazepine administration does not induce sleep (Edgar *et al.* 1993), but the hypnotic effect is restored if the SCN-lesioned animal is sleep deprived before drug administration. Benzodiazepines thus may facilitate the release of a sleep debt accumulated during wakefulness rather than producing de novo sleep (Mignot *et al.* 1992).

The effects of benzodiazepines on sleep architecture are well known. Most benzodiazepines decrease sleep latency (i.e., the amount of time it takes to fall asleep), especially when use is first initiated, and reduce the number of awakenings (Table 44-1). All benzodiazepines increase the time spent in stage 2 sleep. Benzodiazepines also affect the quality of the SWS pattern. Thus, stages 3 and 4 sleep are suppressed and remain so during the period of drug administration. The decrease in stage 4 sleep is accompanied by a reduction in nightmares.

TABLE 44-1. Comparative effects of benzodiazepines and barbiturates on sleep parameters

Parameter	Benzodiazepines	Barbiturates

Note. REM = rapid eye movement sleep; | = increased; | = decreased.

Parameter	**Benzodiazepines**	**Barbiturates**
Total sleep time	| tolerance with short-acting agents	| rapid tolerance
Stage 2, %	|	|
Slow-wave sleep (stages 3 and 4), %	|	| (slight)
REM latency	|	|
REM, %	| (slight)	|
Withdrawal	Rebound insomnia with short-acting agents Carryover effectiveness with long-acting agents REM rebound (slight)	REM rebound Rebound decrease in stage 2 and total sleep time

Note. REM = rapid eye movement sleep; | = increased; | = decreased.

Most benzodiazepines increase REM latency. The time spent in REM sleep is usually shortened; however, the reduction in percentage of REM sleep is minimal because the number of cycles of REM sleep usually increases late in the sleep time. Despite the shortening of SWS and REM sleep, the net effect of benzodiazepines is usually an increase in total sleep time, so that the person feels that the quality of sleep has improved. Furthermore, the hypnotic effect is greatest in subjects with the shortest baseline total sleep time.

If the benzodiazepine is discontinued after 3-4 weeks of nightly use, a rebound in the amount and density of REM sleep and SWS may occur.

However, this is not a consistent finding.

Because long-acting benzodiazepine hypnotics impair daytime performance and increase the risk of falls in older adults, several shorter-acting benzodiazepines are the preferred choice for them (see section "General Considerations in the Pharmacological Treatment of Insomnia" later in this chapter). However, it has been found that short-acting benzodiazepines can induce rebound insomnia (a worsening of sleep difficulty beyond baseline levels on discontinuation of a hypnotic) (Kales *et al.* 1979), rebound anxiety, anterograde amnesia, and even paradoxical rage (Figure 44-7). Many other factors, such as the subtype of insomnia being treated and the dosage and duration of treatment, are also important in explaining the occurrence of these specific side effects, which also may occur with longer-acting benzodiazepines. Nevertheless, enthusiasm for shorter-acting compounds has been tempered by the discovery of these adverse effects.

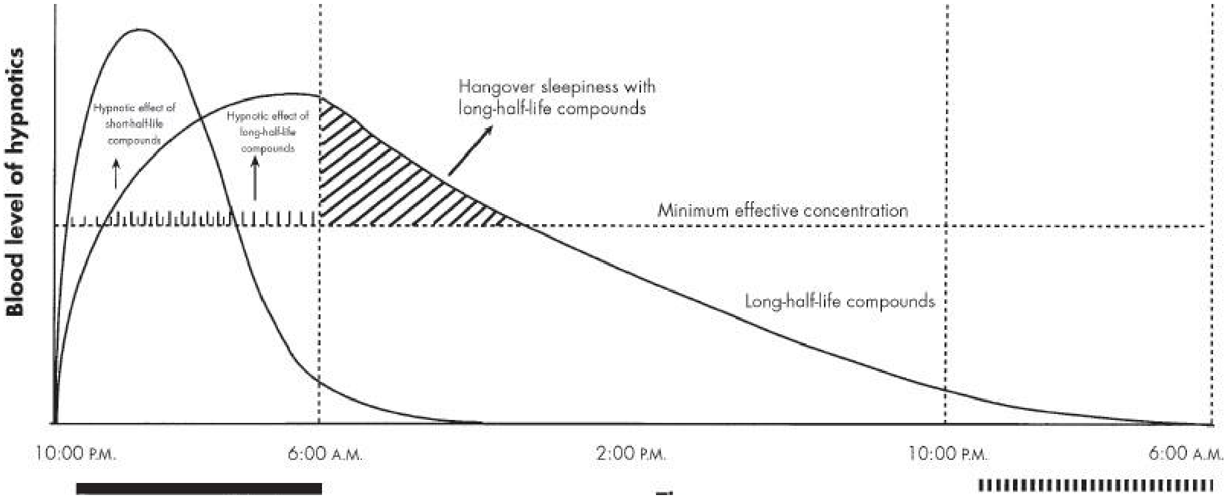

FIGURE 44-7. Duration of action of hypnotics and hangover and rebound insomnia effects.

Hypnotics with long half-lives may impair daytime performance the day after drug administration, whereas short-acting compounds may induce rebound insomnia on discontinuation.

Indications and Efficacy

Benzodiazepines are the drug treatment of choice in the management of anxiety, insomnia, and stress-related conditions. Although none of the currently available compounds has any significant advantage over the others, some drugs can be selected to match the patient's symptom patterns to their pharmacokinetics. If a patient has a persistently high level of anxiety, one of the precursors of desmethyldiazepam, such as diazepam or clorazepate, is most appropriate. Patients with fluctuating anxiety may prefer to take a shorter-acting compound, such as oxazepam or lorazepam, when stressful circumstances occur or are expected.

The indications for nonbenzodiazepine hypnotics are equivalent to those of benzodiazepine hypnotics but may be more specific, depending on the pharmacological properties of each compound.

An ideal hypnotic should induce sleep rapidly without producing sedation the next day. Both flurazepam and nitrazepam have inappropriately long half-lives as hypnotics unless a persistent anxiolytic effect is desired the next day (see Figure 44-7). Even in such situations, diazepam given as a single dose at night may be suitable. Oxazepam penetrates too slowly for a dependable hypnotic effect (slow onset of action). Both lorazepam and temazepam are appropriate treatments for insomnia, but these medications are recommended for short-term use due to withdrawal symptoms (Table 44-2). Triazolam is the shortest-acting hypnotic available. When very small doses of benzodiazepines (which are assumed to have no significant hypnotic action) are administered to patients with insomnia, sleep quality often improves greatly, and usually it is not necessary to prescribe a benzodiazepine at a hypnotic dose as a first-choice treatment.

TABLE 44-2. Pharmacokinetic properties of GABA-enhancing hypnotic compounds most commonly used in the United States

Hypnotic compounds	Usual dose (mg)	T_{max} (hours)[a]	Half-life (hours)[b]	Active metabolites
Benzodiazepines				
Flurazepam (Dalmane)	15-30	0.5-1.0	48-150	*N*-Desalkylflurazepam
Quazepam (Doral)	7.5-15	2	48-120	2-Oxoquazepam, *N*-dealkyl-2-oxoquazepam
Estazolam (ProSom)	1-2	4.9	18-30	1-Oxoestazolam
Lorazepam (Ativan)	2-4	0.8-1.0	10-20	None
Temazepam (Restoril)	15-30	1.5	8-20	None
Triazolam (Halcion)	0.125-0.25	1.3	2-6	None
Nonbenzodiazepines				
Zolpidem (Ambien)	5-10	0.8	1.5-2.4	None
Zopiclone (Imovane in Canada)	3.75-7.5	1.5	5-6	*N*-Oxide zopiclone (weak agonist)
Eszopiclone (Lunesta)	1-3	1	6-9	*S*-Desmethylzopiclone (weak agonist)
Zaleplon (Sonata)	5-20	1.0	1.0-2.5	None

[a] T_{max} is the time required to reach maximal (peak) plasma concentration.

[b] Half-life is the time required by the body to metabolize or inactivate half the amount of a substrate taken.

Benzodiazepines can increase the frequency of apneic episodes and exacerbate oxygen desaturation both in healthy subjects and in subjects with chronic bronchitis (Geddes *et al.* 1976). Although many reports suggest that benzodiazepines are safe for patients with obstructive sleep apnea, some authors disagree, and it seems wise to avoid hypnotics for patients with severe sleep apnea. Another contraindication is myasthenia gravis, a condition in which muscle relaxation with benzodiazepines can exacerbate muscle atonia.

Side Effects and Toxicology

When a benzodiazepine is taken at high dosages, tiredness, drowsiness, and profound feelings of detachment are common but can be minimized by a careful dosage adjustment. Headache, dizziness, ataxia, confusion, and disorientation are less common except in older adults. A marked potentiation of the depressant effect of alcohol occurs. Other less common side effects include weight gain, skin rash, menstrual irregularities, impairment of sexual function, and (very rarely) agranulocytosis.

Although otherwise asymptomatic individuals clearly show mental impairment with benzodiazepines, the situation with anxious patients is more complex. Because anxiety itself interferes with mental performance, alleviation of anxiety may result in improved functioning, which more than compensates for the direct drug-related decrement. The effects in some patients may be complex and unpredictable, even at low dosages.

Tolerance and Dependence

The fact that some patients gradually increase the dosage suggests tolerance, but increases in dosage are sometimes related to particularly stressful crises.

Dependence, both psychological and physical, occurs with benzodiazepines as with other sedative-hypnotics. Abrupt discontinuation results in withdrawal phenomena such as anxiety, agitation, restlessness, and tension, which are usually delayed for several days because of the long half-life of the major metabolite, desmethyldiazepam. Even without an increased dosage, some patients have withdrawal effects. Psychological dependence is also common, based on the high incidence of repeated prescriptions, but it is mild, and the drug-seeking behavior is much less persistent with benzodiazepines than with barbiturates.

Use During Pregnancy and Lactation

Because the safety of benzodiazepines in early pregnancy has not been established, use of these compounds should be avoided unless absolutely necessary. Diazepam is secreted in breast milk and may make the infant sleepy, unresponsive, and slow to feed.

Overdose

The benzodiazepines are very widely prescribed, so it is not surprising that they are used in many suicide attempts. For adults, overdoses of benzodiazepines reportedly are not fatal unless alcohol or other psychotropic drugs are taken simultaneously. Typically, the patient falls asleep but is arousable and wakes after 24-48 hours. Treatment is supportive. A stomach pump is usually more punitive than therapeutic, and dialysis is usually ineffective because of high plasma binding.

Barbiturates

History and Discovery

Barbital, one of the derivatives of barbituric acid, was introduced in 1903 and soon became extremely popular in clinical medicine because of its sleep-inducing and anxiolytic effects (Maynert 1965). In 1912, phenobarbital was introduced as a sedative-hypnotic. Since then, more than 2,500 barbiturate analogs have been synthesized, about 50 of which have been made commercially available and only 20 of which remain on the market.

The success of the partial separation of anticonvulsant from sedative-hypnotic properties led to the development of nonsedative anticonvulsants such as phenytoin in the late 1930s and trimethadione in the early 1940s. The success of barbiturates as sedative-hypnotics was largely overshadowed by the discovery of the benzodiazepines in the late 1960s. With pharmacological properties very similar to those of barbiturates, the benzodiazepines have a much safer pharmacological profile. Thus, benzodiazepines have replaced barbiturates in many instances, especially for psychiatric conditions in which suicide is a possibility.

Structure-Activity Relations

Derivatives of barbituric acid, the parent compound of all barbiturates, do not dissolve readily in water but are quite soluble in nonpolar solvents. In general, structural changes that increase liposolubility also decrease these compounds' duration of action, decrease the latency to onset of activity, accelerate metabolic degradation, and often increase hypnotic potency.

Compared with barbituric acid derivatives with methyl groups at position 5, those with large aliphatic groups at this position have greater activity but a shorter duration of action. However, when aliphatic groups have more than seven carbons, they lose their hypnotic activity and tend to exhibit convulsant activity. Methylation of the 1-*N* atom increases liposolubility and shortens duration of action, and desmethylation may increase the duration of action (Rall 1990).

Pharmacological Profile and Mechanism of Action

The main effects of barbiturates are sedation, sleep induction, and anesthesia. Some barbiturates, such as phenobarbital, also have selective anticonvulsant properties. The mechanisms of action of barbiturates are complex and still not fully understood. Nonanesthetic dosages of barbiturates generally suppress polysynaptic responses. Pertinent to their sedative-hypnotic effects is the fact that the mesencephalic reticular activating system is extremely sensitive to these drugs (Killam 1962). The synaptic site of inhibition is either postsynaptic (e.g., at the level of cortical and cerebellar pyramidal cells and in the cuneate nucleus, substantia nigra, and thalamus relay neurons) or presynaptic (e.g., in the spinal cord). This inhibition occurs only at synapses where physiological inhibition is GABAergic but not glycinergic or monoaminergic. Thus, barbiturates, like benzodiazepines, specifically potentiate GABA-mediated inhibitory processes in the brain. However, it remains unclear whether all of the effects of barbiturates are entirely mediated by GABAergic mechanisms.

Barbiturates do not displace benzodiazepines from their binding sites; instead, barbiturates enhance benzodiazepine binding by increasing the affinity of the receptor for benzodiazepines (Leeb-Lundberg *et al.* 1980). They also enhance the binding of GABA and its agonists to specific binding sites (Asano and Ogasawara 1981). These enhancement effects are almost completely dependent on the presence of chloride or other anions that are known to permeate the chloride channels associated with the GABA receptor complex, and they are competitively antagonized by picrotoxin (a convulsant) (Olsen *et al.* 1978).

The molecular correlations of the barbiturate acting sites on the $GABA_A$ receptor also have been studied. However, neither the sequences involved in the binding of GABA and other direct receptor agonists nor the sequence involved in the action of benzodiazepines is of vital importance to barbiturate function (Amin and Weiss 1993). Whereas some earlier reports suggested that the b subunit alone may form a site for barbiturates (Sanna *et al.* 1995), recent studies attempting to identify structural characteristics and binding sites have found that barbiturates bind to the $GABA_A$ receptor at multiple homologous transmembrane pockets at the subunit interfaces (Chiara *et al.* 2013). Although there is still much to be learned, new molecular experimental approaches hold great promise for resolving the most important pharmacological questions regarding which molecular species are important for the anticonvulsant, sedative, anesthetic, and toxic actions of the barbiturates.

Pharmacokinetics and Disposition

For hypnotic use, barbiturates usually are administered orally. Barbiturates are rapidly absorbed in the stomach, and their absorption decreases when the stomach is full.

Barbiturates are metabolized mainly in the liver. Oxidation of the larger of the two side chains at position 5 is a major catabolic pathway. It generally produces inactive polar metabolites that are rapidly excreted in the urine (Rall 1990). Changes in liver function can markedly alter the metabolic rate. Chronic administration leads to pharmacokinetic tolerance, even when low or infrequent doses of barbiturates are used (see subsection "Drug-Drug Interactions" later in this section).

In general, liposolubility decreases both latency to onset of action and duration of action. Thiopental, for example, enters the CNS quickly and is used to rapidly induce anesthesia; barbitone crosses into the brain so slowly that it is inappropriate as a hypnotic drug.

Effects on Stages of Sleep

Barbiturates decrease sleep latency; however, they also slightly increase fast electroencephalogram activity during sleep. Barbiturates decrease body movements during sleep. Stage 2 sleep increases, whereas stage 3 and stage 4 SWS generally decrease (except for some patients who have anxiety and patients who are addicted to barbiturates; see Table 44-1). REM sleep latency is prolonged, and both the total time spent in REM sleep and the number of REM cycles are diminished. With repeated nighttime administration (i.e., taking a new dose before elimination of the previous dose) of barbiturates, drug tolerance to the effects on sleep occurs in a few days. Discontinuation of barbiturates may lead to insomnia and to disrupted sleep patterns (with a decrease in stage 2 sleep and increases in REM sleep) (Kay *et al.* 1976).

Indications and Efficacy

Although clinical trials have shown that the barbiturates have sedative and hypnotic properties, barbiturates generally compare poorly with benzodiazepines. The patient feels "drugged" the next day, and there is always the risk of fatal overdose because of the depressant effect on respiration. The therapeutic dosage of barbiturates may cause fatal respiratory depression in patients with sleep apnea; therefore, barbiturate use is contraindicated for such patients. Because of these risks, many clinicians have stopped using barbiturates as hypnotics and sedatives (one exception is in the treatment of severe psychomotor excitation) and prescribe them only as anticonvulsants.

Barbiturates also have been administered intravenously to facilitate patient interviews (i.e., amobarbital interview).

Because they enhance porphyrin synthesis, barbiturates are contraindicated for patients with porphyria. Liver function should be checked before and during drug administration. Liver dysfunction can significantly prolong the sedative effects of these drugs and may lead to fatal overdose.

Side Effects and Toxicology

For many patients who are prescribed barbiturates, it is difficult to control symptoms without causing oversedation. Patients typically oscillate between anxiety and torpor. Mental performance is often impaired, and patients should not drive or operate dangerous machinery.

Patients whose conditions have been stabilized for years with barbiturates must be considered drug dependent. Withdrawal leads to anxiety, agitation, trembling, and, frequently, convulsions. Substitution with a benzodiazepine that can be withdrawn more easily later is often successful.

Tolerance and Dependence

Tolerance to barbiturates occurs rapidly and is a result of both pharmacokinetic factors (e.g., liver enzyme induction) and pharmacodynamic factors (e.g., neuronal adaptation to chronic drug administration). Cross-tolerance develops to alcohol, gas anesthetics, and other sedatives, including benzodiazepines.

Psychological dependence (i.e., drug-seeking behavior) is common. Patients typically visit several physicians to obtain more barbiturates. Physical dependence may be induced by a dosage of 500 mg/day. Intoxication may occur, as evidenced by impaired mental functioning, emotional instability, and neurological signs. Abrupt discontinuation after high dosages is likely to induce convulsions and delirium. After normal dosages, withdrawal phenomena include anxiety, insomnia, restlessness, agitation, tremor, muscle twitching, nausea and vomiting, orthostatic hypotension, and weight loss.

Overdose

An overdose of barbiturates leads to fatal respiratory and cardiovascular depression. Suicide attempts often involve overdoses of barbiturates, taken either alone or in combination with alcohol or other psychotropic drugs, particularly tricyclic antidepressants. These suicide attempts, unfortunately, are often successful. Depending on local factors such as proximity to a hospital and expertise of staff in intensive emergency care, death occurs in 0.5%-10% of these cases. Severe poisoning results at 10 times the usual hypnotic dosage, and twice that amount may be fatal.

Drug-Drug Interactions

Barbiturates used with other CNS depressants can cause severe depression. Ethanol is the drug most frequently used in combination with barbiturates, and interactions with antihistaminic compounds are also common. Monoamine oxidase inhibitors and methylphenidate also increase the CNS depressant effect of barbiturates.

Barbiturates may increase the activity of hepatic CYP enzymes twofold to threefold. Clinically, this change is particularly important for patients who are also receiving metabolic competitors such as warfarin or digitoxin, for which careful control of plasma concentrations is vital (Rall 1990).

Other Sedative-Hypnotic Compounds

Table 44-3 summarizes the pharmacological properties of some of the newer classes of hypnotic compounds, including orexin (hypocretin) receptor antagonists, melatonin receptor agonists, and sedative antidepressants with H_1 antagonism.

TABLE 44-3. **Pharmacokinetic properties of newer classes of hypnotic compounds most commonly used in the United States**

Hypnotic compounds	Mechanisms	Usual dose (mg)	T_{max} (hours)^a	Half-life (hours)^b	Active metabolites
Melatonergics					
Melatonin (Circadin^c)	Melatonin receptor agonist	0.5-5.0 (2^c)	0.83 (1.6-2.6^c)	0.75 (3.5-4.0^c)	N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), N^1-acetyl-5-methoxykynuramine (AMK)
Ramelteon (Rozerem)	Melatonin receptor agonist	8	0.75	1.0-2.6	M-II
Tasimelteon (Hetlioz)	Melatonin receptor agonist	20	2	1.3-3.7	None
Orexin receptor antagonists					
Suvorexant (Belsomra)	Orexin receptor antagonist	10-20	2	12	None
Lemborexant (Dayvigo)	Orexin receptor antagonist	5-10	1-3	17-19	M10 (weak antagonist)
Antidepressant sedatives					
Doxepin (Silenor)	H_1 receptor antagonist	3-6	3.5	15.3	*N*-desmethyldoxepin

5-HT_{2C} = 5-hydroxytryptamine (serotonin) type 2C receptor; H_1 = histamine type 1 receptor.

[a] T_{max} is the time required to reach maximal (peak) plasma concentration.

[b] Half-life is the time required by the body to metabolize or inactivate half the amount of a substrate taken.

[c] Prolonged-release tablet.

Hypnotic compounds	Mechanisms	Usual dose (mg)	T_{max} (hours)[a]	Half-life (hours)[b]	Active metabolites
Agomelatine (Valdoxan in EU)	Melatonin receptor agonist; 5-HT_{2C} receptor antagonist	25-50	0.5-4.0	1-2	None

5-HT_{2C} = 5-hydroxytryptamine (serotonin) type 2C receptor; H_1 = histamine type 1 receptor.

[a] T_{max} is the time required to reach maximal (peak) plasma concentration.

[b] Half-life is the time required by the body to metabolize or inactivate half the amount of a substrate taken.

[c] Prolonged-release tablet.

Alcohol-Type Hypnotics

The alcohol-type hypnotics include the chloral derivatives, of which chloral hydrate (0.5-1.0 g), clomethiazole (192 or 384 mg), and ethchlorvynol (0.5-1.0 g) are still used occasionally by older adults. Chloral hydrate is metabolized to another active sedative-hypnotic, trichloroethanol. These drugs have short half-lives (~ 4-6 hours) and decrease sleep latency and number of awakenings; SWS is slightly depressed, but overall REM sleep time is largely unaffected. Chloral hydrate and its metabolite have an unpleasant taste and frequently cause epigastric distress and nausea. Undesirable side effects include light-headedness, ataxia, and nightmares. Chronic use of these drugs can lead to tolerance and occasionally to physical dependence. As with barbiturates, overdose can lead to respiratory and cardiovascular depression, and therapeutic use of these drugs has largely been superseded by the use of benzodiazepines.

Gamma-Hydroxybutyrate/Sodium Oxybate

g-Hydroxybutyrate (GHB) is a hypnotic agent that has been used mostly in the treatment of insomnia for narcoleptic patients (Scrima *et al.* 1990). A small amount of GHB naturally also exists in the CNS (Bessman and

Fishbein 1963). The drug is rarely used in other indications and is often abused. GHB was classified as a Schedule I controlled substance in March 2000 in the United States, but in July 2002, the drug's sodium salt form, sodium oxybate (Xyrem), was approved by the FDA for the treatment of narcolepsy, and a combination calcium, magnesium, potassium, and sodium oxybate formulation (Xywav) was approved in 2021. Nighttime administration of GHB (20-40 mg/kg) reduces excessive daytime sleepiness associated with narcolepsy. The compound promotes SWS and REM sleep (Lapierre *et al.* 1990), but its effects on sleep architecture are short-lasting, and repeated administration usually is necessary during the night. GHB also is used for the treatment of cataplexy in narcolepsy, although the mechanisms of GHB's effect on cataplexy remain unknown.

The physiological significance of a brain GHB signaling pathway and the detailed mechanisms of many actions of exogenous GHB remain unclear. Exogenously administered GHB induces a wide range of neuropharmacological actions, including sedation, memory impairment, an increase in sleep, seizures, dependence or abuse, and coma (Wong *et al.* 2004). GHB has long been known to have an effect on dopamine systems in the brain and probably inhibits dopamine release (Vayer *et al.* 1987).

Most of these actions of exogenous GHB have been shown to be mediated, either fully or in part, by GABA$_{\text{B}}$ receptors (Castelli *et al.* 2004; Maitre 1997; Wong *et al.* 2004). In 2003, the cloning of a putative GHB receptor was reported (Andriamampandry *et al.* 2003).

Despite these findings, the physiological significance of a brain GHB signaling pathway is still unknown, and there is an urgent need for a well-validated functional assay for GHB receptors. Moreover, as GHB can also be metabolized to GABA, it remains to be seen whether the many GABA$_{\text{B}}$ receptor-mediated actions of GHB are caused by GHB itself acting directly on GABA$_{\text{B}}$ receptors or by a GHB-derived GABA pool (or both) (Wong *et al.* 2004).

Antihistamines

Antihistamines such as promethazine (25-50 mg), diphenhydramine (25-50 mg), and doxylamine (25 mg) are sometimes prescribed as sleep inducers. They decrease sleep latency but do not increase total sleep time (see Reite *et al.* 1997). These compounds are especially useful for patients who cannot sleep well because of acute allergic reactions or itching. Because sedative antihistamines lack abuse potential, they also may be a good choice for people with substance use disorders. However, rapid tolerance is a problem.

In April 2008, doxepin hydrochloride (marketed under the trade name Silenor), a tricyclic antidepressant with histamine$_1$ (H_1) receptor antagonism, received FDA approval for the treatment of insomnia (see Table 44-3). Doxepin (as Sinequan, 3 mg and 6 mg) reduces wake after sleep onset and prolongs total sleep time (Markov and Doghramji 2010).

Low-dose doxepin has a terminal half-life of 15.3 hours, and the median time to peak plasma concentration (T_{max}) of doxepin 6 mg is 3.5 hours (Atkin *et al.* 2018). The *N*-desmethyl metabolite of doxepin, *N*-desmethyldoxepin, is pharmacologically active (Kemp *et al.* 1985). Several other selective H_1 receptor blockers and H_1 receptor reverse agonists are under development for use as hypnotics.

GABA Reuptake Receptor Inhibitor

Tiagabine is a GABA reuptake receptor (GAT-1) inhibitor that allows increased GABA concentration at the synaptic level of the CNS (Mathias *et al.* 2001). Tiagabine has been shown to prolong GABA-mediated inhibitory postsynaptic potentials. Tiagabine is in the class of medications called anticonvulsants and is used in combination with other medications to treat partial seizures. Tiagabine (4-16 mg) has been shown to produce a dose-dependent increase in SWS in older adults and patients with primary insomnia (Walsh *et al.* 2006). Doses as low as 10 mg increase the power density of slow electroencephalographic oscillations and also increase the percentage of SWS from 15% to 24% (Mathias *et al.* 2001). Tiagabine, originally approved by the FDA in 1997 as an adjunctive treatment for partial seizures, may be a compound of interest for sleep disorders; however, it has not received FDA approval for the treatment of insomnia.

Melatonin and Melatonin Receptor Agonists

Melatonin

Melatonin is a neurohormone produced by the pineal gland during the dark phase of the day-night cycle. The terminal half-life of melatonin is 45 minutes, and its median T_{max} is 50 minutes (Harpsoe *et al.* 2015). Melatonin has active metabolites such as *N*1-acetyl-*N*2-formyl-5-methoxykynuramine and *N*1-acetyl-5-methoxykynuramine (Hardeland and Pandi-Perumal 2005). In animals, melatonin has been implicated in the circadian regulation of sleep and in the seasonal control of reproduction. Studies suggest that melatonin administration may have some therapeutic effects in various disturbances of circadian rhythmicity, such as those related to jet lag (Arendt *et al.* 1987), shift work (Folkard *et al.* 1993), non-24-hour sleep-wake cycle in blind people (Arendt *et al.* 1988), and delayed sleep phase insomnia (Dahlitz *et al.* 1991), with few side effects (e.g., headaches or nausea). High dosages of melatonin (3-100 mg), which increase serum melatonin levels far beyond the normal nocturnal range, have been suggested to produce hypnotic effects in humans (Dollins *et al.* 1994). Lower and more physiological dosages of melatonin (e.g., 0.3 mg) might also be active (Zhdanova *et al.* 2001).

In humans, the production of melatonin during the dark period declines with age; this effect parallels declines in sleep quantity and quality (van Coevorden *et al.* 1991), especially in older adults with insomnia (Haimov *et al.* 1994; Mishima *et al.* 2001). These findings appear to suggest that deficiencies in nocturnal melatonin secretion might contribute to disrupted sleep in older adults; thus, melatonin may be particularly beneficial for insomnia in this population. Indeed, some studies reported favorable effects with supplementary administration of melatonin for older adults with disturbances in sleep maintenance (Garfinkel *et al.* 1995; Haimov *et al.* 1995). However, several studies reported contradictory findings indicating no significant relation between physiological melatonin secretion levels and sleep maintenance parameters (Hughes *et al.* 1998; Lushington *et al.* 1998; Youngstedt *et al.* 1998; Zeitzer *et al.* 1999) and no significant therapeutic effect of melatonin replacement on sleep maintenance in older adults with insomnia (Hughes *et al.* 1998).

One of the difficulties in establishing the therapeutic efficacy of melatonin is its short half-life (~ 45 minutes) (Harpsoe *et al.* 2015). Bedtime melatonin administration (1-3 mg) reduces sleep latency but has few objective effects on sleep architecture. It is also unclear whether the hypnotic effect from a physiological or pharmacological dose represents a direct effect on sleep, an indirect effect on circadian timing that subsequently gates the release of sleep, or both. Finally, very few double-blind, placebo-controlled studies have been done, and most current reports are confounded by strong placebo effects in the context of a melatonin fad. Melatonin might be an effective hypnotic in some indications, but better-controlled studies are needed to establish its efficacy in specific indications. The purity of products sold as health supplements is also a problem, and the long-term effects of melatonin administration in humans are unknown.

Circadin is a prolonged-release formulation of melatonin, designed to mimic the release pattern of endogenous melatonin by releasing melatonin gradually over 8-10 hours (Laudon and Frydman-Marom 2014), because the half-life of melatonin taken orally is very short (~ 45 minutes). Circadin has been used in multiple clinical trials, showing statistically significant and clinically meaningful efficacy in insomnia parameters (Laudon and Frydman-Marom 2014; Lemoine *et al.* 2007; Wade *et al.* 2010). Its use as a prescribed drug has been approved in some countries (e.g., Australia, New Zealand), but not in the United States. Circadin is fully absorbed, but bioavailability is only about 15% because of its high first-pass hepatic degradation, primarily through CYP1A2. After oral ingestion, maximal melatonin concentrations in the blood are attained after 0.75 hour in fasting and 3 hours in nonfasting states. Circadin is eliminated mainly as sulfated and glucuronide conjugates after biotransformation in the liver and only partly (2%) as unchanged melatonin. The terminal half-life of Circadin is 3.5-4 hours, and T_{max} requires 1.6 hours (fasting) to 2.6 hours (nonfasting) to occur (New Zealand Medicines and Medical Devices Safety Authority 2011).

Melatonin Receptor Agonists

There are at least three subtypes of melatonin receptors with high (MT_1 or MT_{1a}) and low (MT_2 or MT_{1b} and MT_3 or MT_{1c}) affinities for this ligand (Dubocovich 1995; Morgan *et al.* 1994; Reppert *et al.* 1994, 1995). The localization of the MT_1 receptor in the SCN, median eminence, and retina in humans and rodents suggests that this receptor is essential for circadian regulation and reproduction, whereas the MT_2 receptor is localized mainly in the retina. Melatonin receptors in the retina probably play an important role in retinal physiology, including circadian regulation (Sengupta *et al.* 2011) and photopigment disc shedding (Besharse and Dunis 1983).

Ramelteon (8 mg), a melatonin receptor agonist with both high affinity for melatonin MT_1 and MT_2 receptors and low affinity for the MT_3 receptor and with a longer half-life than melatonin, was approved by the FDA in July 2005 for the treatment of insomnia characterized by difficulty with sleep onset (see Kuriyama *et al.* 2014; Takeda Pharmaceuticals America, Inc. 2010). The terminal half-life of ramelteon is 1-2.6 hours, and its median T_{max} is 45 minutes (Zammit 2007). Ramelteon is metabolized primarily to the active metabolite M-II (Nishiyama *et al.* 2014). Ramelteon does not show any appreciable binding to $GABA_A$ receptors, which are associated with anxiolytic, myorelaxant, and amnesic effects. Ramelteon has not been demonstrated to produce dependence and has shown no potential for abuse, and the withdrawal and rebound insomnia typically seen with other GABA modulators do not appear to be present.

Animal studies demonstrated that the sleep-enhancing effects of ramelteon are not associated with reductions in REM sleep (Miyamoto *et al.* 2004). Ramelteon is currently the only nonscheduled prescription drug for the treatment of insomnia available in the United States. It has no appreciable affinity for receptors that bind neuropeptides, cytokines, serotonin, dopamine, norepinephrine, acetylcholine, and opiates. It also does not interfere with the activity of any known enzymes in standard panels. The activity of ramelteon at the MT_1 and MT_2 receptors, especially those in the SCN, is believed to contribute to its sleep-promoting properties, as these receptors, acted upon by endogenous melatonin, are thought to be involved in maintenance of the circadian rhythm underlying the normal sleep-wake cycle.

The activity of ramelteon is similar to the biological action of melatonin. No published studies have reported comparative data on whether ramelteon is more or less safe or effective than melatonin, a much less expensive drug widely available in the United States without a prescription.

Recent studies have reported findings suggesting that melatonin (0.5 mg) or ramelteon (8 mg) can prevent delirium in older adults (Al-Aama *et al.* 2011; Hatta *et al.* 2014). Although significant decline in melatonin levels during aging has been reported by many investigators (Srinivasan *et al.* 2006), modes of action for preventing delirium in older adults are not known.

Another MT_1/MT_2 receptor agonist, tasimelteon (Rajaratnam *et al.* 2009), was approved by the FDA in January 2014 for the treatment of non-24-hour sleep-wake disorder (N24HSWD) in totally blind people (Vanda Pharmaceuticals Inc. 2014; see also Sack *et al.* 1991). The terminal half-life of tasimelteon is 1.3-3.7 hours, and the median T_{max} is 2 hours (Bonacci *et al.* 2015). When taken as a treatment for N24HSWD, similar to melatonin, the patient may experience improved sleep timing. The metabolism of tasimelteon consists primarily of oxidation at multiple sites and oxidative dealkylation. CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon. Phenolic glucuronidation is the major phase II metabolic route. Major metabolites had 13-fold or less binding affinity at melatonin receptors compared with tasimelteon. Therefore, the metabolites do not contribute to its efficacy. Tasimelteon has been developed for the treatment of circadian rhythm sleep disorders (Nishimon *et al.* 2019). Approximately 55%-70% of totally blind patients are thought to have nonentrained rhythms, and if they report periodic difficulties with sleep or daytime alertness they are diagnosed as having N24HSWD ("free running") (Nishimon *et al.* 2019). Phase II and III studies have been conducted in transient insomnia associated with shifted sleep and wake time (Hardeland 2009). In the Phase II study, tasimelteon reduced sleep latency, increased sleep efficiency compared with placebo, and dose-dependently advanced plasma melatonin rhythm. In the Phase III study, tasimelteon improved sleep latency, sleep efficiency, and wake after sleep onset. The frequency of adverse events in both studies was comparable to that of placebo (Mulchahey *et al.* 2004).

Agomelatine is a melatonin MT_1 and MT_2 receptor agonist and a weak serotonin$_{2C}$ (5-HT_{2C}) antagonist. In addition to its antidepressant effects, agomelatine improved sleep quality and reduced waking after sleep onset in depressed patients (Taylor *et al.* 2014). Whereas the sleep-promoting effects of agomelatine can clearly be ascribed to its melatonergic activity, the antidepressant function has been ascribed to 5-HT_{2C} receptor antagonism. However, because of agomelatine's short half-life and low 5-HT_{2C} affinity, it is disputed to what extent the 5-HT_{2C} antagonism contributes to its therapeutic effect (Millan *et al.* 2011). After ingestion, agomelatine is rapidly and well absorbed (80%) irrespective of food intake. The peak plasma levels are reached in 0.5-4 hours, and plasma half-life is short (1-2 hours) (De Berardis *et al.* 2015). It is highly protein bound (> 95%) and is metabolized in the liver, primarily through CYP1A2, to form inactive metabolites that are mainly (80%) excreted in the urine. A major metabolite, 3-hydroxy-7-desmethyl-agomelatine, has low affinity for MT_1, MT_2, and 5-HT_{2C} receptors (Dolder *et al.* 2008). Because of the antidepressant effects of agomelatine, this drug may also be used for insomnia associated with depressive symptoms in older adults and is well tolerated in depressed patients older than 65 years (Heun *et al.* 2013).

Melatonin receptor agonists may be useful for patients who experience insomnia due to shift work or jet lag, as well as for delayed sleep phase syndrome or advanced sleep phase syndrome, as beneficial effects of melatonin were reported in these conditions.

Orexin (Hypocretin) Receptor Antagonists

Orexin A (or hypocretin 1) and orexin B (or hypocretin 2) are newly discovered hypothalamic neuropeptides that play critical roles in the promotion and maintenance of wakefulness and in the pathophysiology of narcolepsy with cataplexy (Nishino 2011; Sakurai *et al.* 1998). In humans, chronic loss of orexin neurons is associated with narcolepsy with cataplexy (i.e., type 1 narcolepsy, as defined by the *International Classification of Sleep Disorders*, 3rd Edition [ICSD-3] [American Academy of Sleep Medicine 2014]). Orexin neurons are presumed to be active during wakefulness and reduce activities during sleep, and two G-protein-coupled receptors for orexin peptides (orexin receptor 1 and orexin receptor 2) have been identified (Nishino 2011; Sakurai *et al.* 1998).

Although attempts to treat human narcolepsy with orexin receptor agonists are still in progress, suvorexant, an orally active dual orexin receptor antagonist, was recently developed and in 2014 was approved for the treatment of adult patients with insomnia characterized by difficulties with sleep onset or sleep maintenance (see Winrow *et al.* 2011; Yang 2014; also see Merck and Co. 2014). The recommended dosage is 10 mg (a maximum of 20 mg once daily), to be taken orally once per night, within 30 minutes of going to bed and with at least 7 hours remaining until the planned waking time.

Suvorexant 15 or 20 mg once daily generally improved sleep maintenance and sleep onset (Jacobson *et al.* 2014). A significantly greater improvement relative to placebo was seen with suvorexant 15 or 20 mg once daily in most objective endpoints at 1 night, 1 month, and 3 months (Jacobson *et al.* 2014). Suvorexant is contraindicated in people diagnosed with narcolepsy, since the consequences of taking orexin receptor antagonists in type 1 (hypocretin deficient) and type 2 (hypocretin nondeficient) narcolepsy are unpredictable (Merck and Co. 2014). Suvorexant is not recommended for patients with liver impairment or for those who are also taking medications that strongly inhibit the liver enzyme CYP3A, such as itraconazole, lopinavir/ritonavir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, or conivaptan (Merck and Co. 2014).

The drug is well tolerated, but adverse effects include sleepiness and fatigue the next day and problems with driving, as well as unusual dreams

(Merck and Co. 2014), and sleep paralysis and hypnagogic/hypnopompic hallucinations may occur with its use. The median T_{max} of suvorexant is 2 hours (in fasting condition), and high-fat food ingestion can delay T_{max} (Cada *et al.* 2015). For suvorexant 10 mg, the mean absolute bioavailability is 82%. Administration of suvorexant with a high-fat meal had no clinical effect on systemic drug exposure but delayed T_{max} by 1.5 hours. Steady state is achieved within 3 days. Suvorexant is metabolized primarily by CYP3A, with a minor contribution by CYP2C19 (Merck and Co. 2014). The main circulating compounds are the unchanged drug and a hydroxyl metabolite, which is not expected to be pharmacologically active. Suvorexant is eliminated primarily in the feces, with recovery of

66% of a radiolabeled dose in the feces and 23% in the urine. The mean elimination half-life of suvorexant is 12 hours (Cada *et al.* 2015).

Concomitant use of suvorexant with other CNS depressant drugs (e.g., benzodiazepines, opioids, tricyclic antidepressants) may result in potentially additive effects; dosage adjustments in either or both drugs may be necessary (Merck and Co. 2014).

Efficacy of suvorexant in delirium prevention was reported in several randomized clinical trials in the ICU or acute care settings (Hatta *et al.* 2017). A recent study has also examined the effects of suvorexant on delirium prevention in everyday clinical settings in a comparison of 84 suvorexant users and 615 suvorexant nonusers (Izuhara *et al.* 2020). Delirium prevalence was significantly lower in suvorexant users than in nonusers (17.9% vs. 32.4%, respectively; $P = 0.007$). Cox regression analysis revealed a significantly lower hazard ratio (0.472; 95% CI: 0.268-0.832; $P = 0.009$) of delirium in suvorexant users than in nonusers. Trazodone also had a preventive effect on delirium (hazard ratio, 0.345; 95% CI: 0.149-0.802; $P = 0.013$).

A study showed that the risk of falls also exists for suvorexant but not ramelteon (Ishibashi *et al.* 2020), and thus it is necessary to carefully prescribe hypnotic drugs under appropriate assessment.

Lemborexant, another dual orexin receptor (OXR) antagonist, has been approved for the treatment of insomnia disorders, and drugs with a distinctive profile (daridorexant) or orexin-2 receptor selectivity (seltorexant) are in development.

In vitro, lemborexant acts as a competitive antagonist at OXR1 and OXR2, with respective IC_{50} values of 6.1 nmol/L and 2.6 nmol/L (Scott 2020; Yoshida *et al.* 2015). The T_{max} ranged from approximately 1 to 3 hours, and the mean effective half-life was 17 hours for 5 mg and 19 hours for 10 mg (Landry *et al.* 2021). A major metabolite of lemborexant (M10) binds with comparable affinity to the parent drug to OXR1 and OXR2 (IC_{50}, 4.2 and 2.9 nmol/L). In December 2019, lemborexant was approved in the United States for the treatment of adults with insomnia characterized by difficulties with sleep onset or sleep maintenance. It is also being investigated for the treatment of irregular sleep-wake rhythm disorder associated with mild to moderate Alzheimer's disease.

Lemborexant improves sleep onset and sleep maintenance for patients with insomnia (Scott 2020). The recommended starting dosage of lemborexant is 5 mg taken once daily immediately before bed. The dosage may be increased to 10 mg if needed; however, patients older than 65 years should be limited to 5 mg once daily. Lemborexant should be taken only if the patient has at least 7 hours to devote to sleep at night. The effectiveness of lemborexant is decreased if it is taken with food, particularly for sleep onset. Lemborexant has been compared with placebo and zolpidem for sleep onset and maintenance in two randomized, double-blind, placebo-controlled studies that included approximately 800 adults (Murphy *et al.* 2017; Yardley *et al.* 2021). It has been shown to improve objective and subjective sleep measures (Murphy *et al.* 2017; Rosenberg *et al.* 2019; Yardley *et al.* 2021). Effects are seen within 1 week and are maintained for at least 12 months; they include faster sleep onset and decreased nighttime awakenings. After 12 months of nightly treatment, patients fell asleep an average of 26 minutes faster with either dosage of lemborexant from a baseline delay of about 1 hour. Lemborexant delays the time to first awakening by about 43 minutes (Yardley *et al.* 2021). In adults older than 55 years, lemborexant decreases time to sleep onset by about 20 minutes, compared with 7.5 minutes with zolpidem extended release ($P < 0.001$). Lemborexant shows a modest improvement over zolpidem in waking after sleep onset, providing an additional 7-9 minutes of sleep before first awakening (Rosenberg *et al.* 2019). Lemborexant has not been studied in shift workers or patients with jet lag.

A meta-analysis examined differences between lemborexant, suvorexant, and zolpidem in efficacy and safety outcomes for treating patients with insomnia (Kishi *et al.* 2020). Primary outcomes were subjective time to sleep onset, subjective total sleep time, and subjective wake after sleep onset at week 1. Four double-blind, randomized controlled trials were identified ($N = 3,237$; mean age 58.0 years). The treatment arm consisted of lemborexant 10 mg/day ($n = 592$), lemborexant 5 mg/day ($n = 589$), suvorexant 20/15 mg/day ($n = 493$), zolpidem tartrate extended release 6.25 mg/day ($n = 263$), and placebo ($n = 1,300$). All active treatments outperformed placebo regarding subjective time to sleep onset at week 1, subjective total sleep time at week 1, and subjective wake after sleep onset at week 1. Although no significant differences were found in discontinuation due to adverse events between each active drug and placebo, lemborexant 10 mg/day and suvorexant 20/15 mg/day were associated with greater daytime somnolence compared with placebo. Lemborexant 10 mg/day had the largest effect size compared with placebo for all primary outcomes, although with a risk of somnolence.

General Considerations in the Pharmacological Treatment of Insomnia

The ICSD is the classification system most commonly used by sleep medicine specialists. The first edition was published in 1990, and the ICSD was subsequently revised in 2005 (ICSD-2) and 2014 (ICSD-3). The sleep disorder chapter in DSM-5 (American Psychiatric Association 2013) also classifies sleep disorders in the same manner as ICSD-3 (American Academy of Sleep Medicine 2014).

Insomnia is a subjective complaint of insufficient, inadequate, or nonrestorative sleep (Buysse and Reynolds 1990). ICSD-3 defines *insomnia* as "a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep and results in some form of daytime impairment" (American Academy of Sleep Medicine 2014). Inadequate sleep causes disturbances in daytime functioning, such as fatigue, mood problems, and impaired performance.

Insomnia is a common symptom. Estimates of its prevalence depend on the definition criteria used and the population studied. As a result of these differences in case definition, prevalence estimates have varied widely, from 10% to 40% (Mai and Buysse 2008), but tend to average about 30% for insomnia and 5%-10% for specific insomnia disorders at (Roth 2007). The current use of hypnotics in the general population is estimated to range between 3.5% and 11.7% (Mellinger *et al.* 1985; Ohayon and Caulet 1996; Ohayon *et al.* 1998; Quera-Salva *et al.* 1991).

Insomnia is a symptom that must be explored clinically before treatment is initiated. Sleep disturbances often indicate a larger psychiatric problem, such as depression. As mentioned earlier, insomnia is a common complaint in older populations, especially in institutional settings. In some cases, environmental factors (e.g., noise) or other sleep disorders (e.g., periodic leg movements, sleep apneas, parasomnias) may be involved.

The older classifications, ICSD-2 and DSM-IV (American Psychiatric Association 1994), considered the sleep disorder "primary insomnia" if it occurred as an independent disorder and "secondary insomnia" when it related to another mental disorder (e.g., depression) or medical condition (e.g., pain). ISCD-3 and DSM-5 pay more attention to coexisting medical conditions in defining sleep disorders (now called sleep-wake disorders), to better emphasize when a person has a sleep disorder warranting independent clinical attention, in addition to any medical and mental disorders that are also present. DSM-5 recognizes that coexisting medical conditions, mental disorders, and sleep disorders (comorbid insomnia) are interactive and bidirectional, and it is not as important to make assumptions about what causes the sleep disorder (Reynolds and O'Hara 2013). That is the reason the diagnosis of primary insomnia has been renamed *insomnia disorder*, in order to avoid the differentiation of primary and secondary insomnia. Insomnia can be transient, lasting a few days or weeks. Or, if it lasts 3 months or more, it can be a chronic disorder, and in such cases it will typically not remit spontaneously. Previous drug developments for insomnia focused on primary insomnia, and clinical trials typically recruited patients with the primary disorder. However, in the majority of cases insomnia is comorbid with other conditions. It has been increasingly recognized in recent years that insomnia increases the risk of hypertension, cardiovascular disease, metabolic disorders, and Alzheimer's dementia, and the presence of these medical conditions exacerbates the insomnia (Roth and Roehrs 2003; Sivertsen *et al.* 2014). The change in the definition of insomnia by ICSD-3 and DSM-5 may also change the approach to insomnia drug development.

Insomnia Classifications Based on Duration

A useful initial approach to a patient with insomnia is to consider the duration of the complaint (acute [transient, short-term] vs. chronic). The duration of insomnia not only suggests its cause but also provides some guidance on how to use hypnotics.

ICSD-3 identifies three distinct types of insomnia: short-term insomnia, chronic insomnia, and other insomnia (when the patient has insomnia symptoms but does not meet criteria for the other two types of insomnia). Previous editions had subclassified chronic insomnia into primary and comorbid types, but these were eliminated in ICSD-3 because the subclassifications did not improve diagnostic accuracy.

Chronic Insomnia Disorder

ICSD-3 consolidates all chronic insomnia diagnoses under a single disorder, chronic insomnia disorder. Chronic insomnia requires a report of a sleep initiation or sleep maintenance problem, adequate opportunity and circumstances to sleep, and daytime consequences as a result of the insomnia symptoms.

To meet diagnostic criteria for chronic insomnia disorder, the patient should have symptoms at least three times per week over a duration of at least 3 months. Since insomnia is a component of many psychiatric and medical conditions, a diagnosis of chronic insomnia disorder should be considered only when the insomnia is very prominent and it requires further evaluation and treatment.

Short-Term Insomnia Disorder

A diagnosis of short-term insomnia must meet the same criteria as chronic insomnia except that the symptoms have been present for less than 3 months. The development is often temporally related to a significant stressor. To make this diagnosis, the insomnia must be an independent focus for the patient or require separate clinical attention. This type of insomnia often resolves when the stressor does, or when the patient develops adequate coping mechanisms or adapts to the stressor (American Academy of Sleep Medicine 2014). However, in some cases this may evolve into chronic insomnia.

Transient insomnias (1-2 days) are also common and are typically caused by an environmental acute stressor, jet lag, or shift work and do not often require pharmacological treatments. However, pharmacotherapy with benzodiazepine hypnotics or other hypnotics may have less risks because dependence on the treatment is unlikely to develop when the therapy lasts less than 10 days.

It is particularly important that transient and short-term (a few days to a few months) insomnias be recognized and treated so that they do not evolve into longer-term, enduring disorders, such as psychophysiological insomnia. In this subtype, the patient begins to worry excessively about his or her sleep, so that what may have begun as a brief period of insomnia during a stressful time transitions into a behaviorally learned chronic sleep disorder that does not resolve once the stressful period is over. In psychophysiological insomnia, daily use of benzodiazepine hypnotics is also dangerous because it may lead to tolerance and dependence. The clinician should provide reassurance regarding the favorable resolution of the stressful event, and the patient should be instructed to use hypnotic medications intermittently to avoid developing tolerance. Education in proper sleep hygiene is also important to reduce the possibility of insomnia evolving into a chronic problem.

Insomnia Classifications Based on Clinical Features

Insomnia also can be classified on the basis of individual clinical features: sleep initiation, sleep maintenance, and termination (early morning awakening). These clinical features are still important because they can be objectively evaluated with polysomnography. Some clinical features are known to be associated with certain clinical conditions, such as nocturnal awaking and early morning wakening in elderly insomnia and early morning wakening in depression. These clinical features also determine the pharmacological target and relevant properties in selecting treatments. For example, the most important pharmacological properties to consider when selecting a hypnotic for treatment are how quickly it acts and how long the effects last (see Table 44-2 for commonly used compounds). The rate of absorption is the most critical factor determining onset of action, and T_{max} is the pharmacological parameter that best predicts onset of action. After absorption, hypnotics are distributed to various organs; distribution and drug elimination influence the duration of action. The elimination half-life (see Table 44-2) usually provides a good first estimate of the duration of action for drugs that have comparable absorption and distribution profiles. Hypnotics with a long duration of action are helpful for patients who have difficulty both initiating and maintaining sleep. One advantage of these long-acting compounds is that rebound insomnia is often delayed and milder if the drugs have to be withdrawn (see Figure 44-7). Patients who have difficulty initiating sleep might prefer short-acting compounds; however, for these compounds, it may be necessary, paradoxically, to switch to longer-acting hypnotics before withdrawing all hypnotic treatment.

A recent study conducted a network meta-analysis of comparisons of the efficacy and safety of hypnotics for insomnia, including total sleep time, sleep latency, and wake after sleep onset, in 24 articles with 5,917 older adults (Chiu *et al.* 2021). Eszopiclone and low-dose doxepin were ranked as the optimal therapy for prolonging objective and subjective total sleep time (+ 26.69 and + 28.19 minutes), respectively, compared with placebo. Zaleplon was the most effective therapy in reducing objective and subjective sleep onset latency ([?] 21.63 and [?] 15.86 minutes) compared with control. Temazepam was the best treatment for objective and subjective wake after sleep onset ([?] 25.29 and [?] 22.25 minutes) compared with control. Low-dose doxepin appeared to be the most effective treatment for increasing objective sleep efficiency (6.08% improvement vs. placebo). Triazolam showed a higher overall risk of adverse events (OR, 1.96, 95% CI: 1.03-3.74) when compared with zaleplon.

The importance of determining whether insomnia is the symptom of an underlying neuropsychiatric condition must be emphasized (see Chapter 58 in this textbook, "Treatment of Insomnia"). If depression is a contributing factor, a sedating antidepressant such as amitriptyline, doxepin, or trazodone can be used either alone or in combination with a hypnotic agent (see Chapter 48, "Treatment of Depression"). Patients with schizophrenia can experience persistent insomnia (affecting both initiation and maintenance of sleep), and antipsychotics with sleep-enhancing effects, such as olanzapine or quetiapine, may be effective therapies (see Chapter 53, "Treatment of Schizophrenia"). For insomnia associated with anxiety disorders, hypnotics supplemented with anxiolytics can be used (see Chapter 50, "Treatment of Anxiety Disorders").

Special Considerations for Insomnia Treatment in Older Adults

Sleep disturbances are very common complaints in old age, and treatment must be initiated carefully in this population. Between 5% and 33% of older adults in North America and the United Kingdom are prescribed a benzodiazepine or a benzodiazepine receptor agonist (e.g., zolpidem, zopiclone, zaleplon) for sleep problems (Aparasu *et al.* 2003; Craig *et al.* 2003; Gottlieb 1990; Jaussent *et al.* 2013), and this segment of the population receives 35%-40% of all sedative-hypnotic prescriptions (Gottlieb 1990).

Before pharmacological therapy is started, all possible causes of insomnia should be examined (e.g., psychophysiological; associated with drugs or alcohol; due to disturbance of the sleep-wake cycle; associated with periodic leg movements, sleep apnea, or other physical or psychiatric conditions). Likewise, before selecting a specific hypnotic, the clinician should consider its pharmacological properties and side effect profile, the patient's medical health and medical history, and the patient's history of sedative-hypnotic use. The special case of melatonin and melatonin receptor agonists was discussed earlier in this chapter (see section "Other Sedative-Hypnotic Compounds"). It is expected that data on the efficacy of orexin receptor antagonists for older adults will be accumulated in the near future.

Hypnotics or their active metabolites often accumulate during chronic use in older adults, and this accumulation may cause cognition problems, disorientation, confusion, and (occasionally) falls. Hypnotics with short or intermediate half-lives are thus recommended, and the lowest dosage possible should be used. Compounds with a short half-life, such as triazolam or zolpidem, may be effective for problems with sleep initiation and sleep fragmentation. Zolpidem has little muscle relaxant effect and may be preferable to triazolam. Compounds with an intermediate hypnotic profile, such as estazolam or temazepam, are also reported to be effective for older adults. Hypnotics with intermediate half-lives may alter daytime performance and memory to a lesser extent and are not as likely to induce rebound insomnia after withdrawal as are regular hypnotics.

Mode of action is another important factor to consider in the selection of compounds to treat insomnia. The older sedative-hypnotics compounds probably act on the executive system for sleep induction (i.e., enhancing GABA-mediated sleep induction). It is still unknown whether benzodiazepine endogenous ligands exist and whether such abnormalities are involved in certain types of insomnias. These classes of compounds may be effective in various insomnias regardless of their causes but do not affect the disease conditions. In contrast, two new classes of hypnotics, orexin receptor antagonists and melatonin receptor agonists, specifically block and enhance endogenous orexinergic and melatonergic neurotransmissions, respectively. In animal experiments, it was reported that orexin receptor antagonists do not increase sleep induction when animals have normal sleep amounts, unlike the classic sedative-hypnotics (Gotter *et al.* 2016). It is also known that orexin receptor antagonists do not induce sleep in orexin-neuron-deficient mouse models (Beuckmann *et al.* 2019; Gotter *et al.* 2016; Mang *et al.* 2012). Therefore, these new classes of compounds may more specifically act on insomnias with abnormalities via orexinergic and melatonergic neurotransmission.

Conclusion

The mechanism of action of most currently available hypnotics (benzodiazepines, barbiturates, alcohol, and recent nonbenzodiazepine hypnotics) involves a modulatory effect of GABAergic activity. These compounds stimulate GABAergic transmission by acting on the $GABA_A$-benzodiazepine-Cl^- macromolecular complex, known to contain multiple modulatory binding sites and many receptor subtypes. This recently discovered molecular diversity within the macromolecular complex suggests that new GABAergic hypnotic compounds, including recently developed nonbenzodiazepine hypnotics with subtype selectivity, may have better side effect profiles.

Other non-GABAergic hypnotics, including mostly sedative antidepressants, antihistamines, melatonin and melatonin receptor agonists, and most recently orexin receptor antagonists, are viable strategies in the treatment of insomnia, especially because these hypnotics may lack some of the hampering side effects often seen with classic GABAergic hypnotics, such as abuse potential and amnesic effects. Their prescription, like that of regular benzodiazepine-like hypnotic compounds, should be guided by the knowledge that insomnia is a heterogeneous condition that should be explored clinically before any pharmacological treatment is initiated.

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CHAPTER 45

Psychostimulants and Wakefulness-Promoting Agents

Charles DeBattista, D.M.H., M.D.

Amphetamine, first discovered in 1887, and the subsequently developed stimulants have been used in clinical psychiatry with varying results. Beyond their use for ADHD, stimulants have been used for symptomatic relief based on their effects on mood and hedonic drive. Research into the use of stimulants as adjunctive agents in the treatment of specific symptoms and syndromes has been increasing. Various common adjunctive psychotherapeutic uses for stimulants, such as depression, have not been well researched, whereas other indications, such as narcolepsy, are backed by considerable clinical data. In this chapter, I review the pharmacology of these medications and their indications (Tables 45-1 and 45-2).

TABLE 45-1. FDA classifications of psychostimulants and wakefulness-promoting agents

Agent	Schedule	Approved for	Medication type	Abuse potential

Note. OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift-work sleep disorder.
Source. Data from *Physicians' Desk Reference*, 60th Edition. Montvale, NJ, Medical Economics Company, 2006.

Agent	Schedule	Approved for	Medication type	Abuse potential
Amphetamine	II	ADHD, narcolepsy	Anorexiant/stimulant	Black box warning
Lisdexamfetamine	II	ADHD, binge eating	Stimulant	Black box warning
Methylphenidate	II	ADHD, narcolepsy	Anorexiant/stimulant ("mild stimulant")	Black box warning
Modafinil	IV	Excessive daytime sleepiness associated with narcolepsy, OSAHS, and SWSD	Wakefulness-promoting agent	Reinforcing
Armodafinil	IV	Excessive daytime sleepiness associated with narcolepsy,	Wakefulness-promoting agent	Reinforcing

Note. OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift-work sleep disorder.
Source. Data from *Physicians' Desk Reference*, 60th Edition. Montvale, NJ, Medical Economics Company, 2006.

Agent	Schedule	Approved for	Medication type	Abuse potential
		OSAHS, and SWSD		

Note. OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift-work sleep disorder.
Source. Data from *Physicians' Desk Reference*, 60th Edition. Montvale, NJ, Medical Economics Company, 2006.

TABLE 45-2. Amphetamine and methylphenidate preparations

Stimulant	Time to effect	Peak (hours)	Duration (hours)	Dosing
Amphetamine preparations				
Adderall[a]	~ 1 hour	3	6 -9	bid
Adderall XR	1-2 hours	7	6 -10	qd (or bid)
Dexedrine	1 hour	3	4 -6	bid or tid
Dexedrine Spansules	1 hour	4	6 -10	qd or bid
Desoxyn (methamphetamine)	40 minutes	1 -3	4 -24	qd, bid, or tid
Vyvanse (lisdexamfetamine)	~ 1 hour	2	9	qd
Methylphenidate preparations				
Methylphenidate	15-30 minutes	1 -2	4 -5	bid or tid
Focalin (dexmethylphenidate)	15-30 minutes	1 -2	4 -5	bid or tid

[a] Amphetamine/dextroamphetamine, 1:3 ratio.

[b] Laser hole in capsule allows passage of drug; osmotically active push layer expels drug.

[c] Rapid-release and continuous-release beads give biphasic response.

Stimulant	Time to effect	Peak (hours)	Duration (hours)	Dosing
Ritalin SR (tablet)	1-2 hours	5	8	qd or bid
Concerta[b]	1-2 hours	6 -8	12	qd or bid
Metadate-CD[c]	1 hour	Biphasic: 1-2 and 4-5	6 -8	qd or bid
Jornay-PM	8-9 hours	14 -16 hours	6 -8	qhs
Azstarys	1-2 hours	2.0 -4.5	6 -8	qd

[a] Amphetamine/dextroamphetamine, 1:3 ratio.

[b] Laser hole in capsule allows passage of drug; osmotically active push layer expels drug.

[c] Rapid-release and continuous-release beads give biphasic response.

Amphetamines

Structure-Activity Relations

Structurally, amphetamine is phenylisopropylamine. Ultimate pharmacological action is determined by alterations to any of the three basic parts of the amphetamine molecule.

Amine Changes

In terms of affecting clinical utility, substitution at the amine group is the most common alteration. Methamphetamine (both L and D isomers), which is characterized by an additional methyl group attached to the amine, making it a secondary substituted amine, is more potent than amphetamine. Usefully, one may think of the amine group as enhancing stimulant-like properties.

Isopropyl Changes

An intact isopropyl side chain appears to be needed in order to maintain the potency of amphetamine. For example, changing the propyl to an ethyl chain creates phenylethylamine, an endogenous neuroamine (a metabolite of the monoamine oxidase inhibitor [MAOI] phenelzine) that has mood-and energy-enhancing properties but less potency and a much shorter half-life than amphetamine (Janssen *et al.* 1999).

Aromatic Changes

Substitutions on the phenyl group are associated with a decrease in amphetamine-like properties. Interestingly, reduction of the phenyl to a cyclohexyl ring reduces the potency, but not the efficacy, of amphetamine properties. Unlike changes at the amine or isopropyl level, additions to the aromatic ring substantially alter the effects of the compound. The most common changes at the aromatic ring are of the methoxy type and are associated with hallucinogenic properties.

Stereospecificity

In recent years there has been renewed interest in drugs that are pure stereoisomers, as opposed to racemic mixtures, especially with the release of dexmethylphenidate (the dextro isomer of methylphenidate) and escitalopram (the levo isomer of citalopram).

In amphetamine isomers, it is true that the dextro form (i.e., dextro isomer, or dextroamphetamine) is almost twice as potent as the levo form (i.e., levo isomer, or levoamphetamine) in promoting wakefulness, but they are of equal potency in reducing cataplexy and rapid eye movement (REM) sleep (Nishino and Mignot 1997). The effect on dopamine reuptake is stereospecific; inhibition in rat brain, striatum, and hypothalamus has been found to be markedly different between the two isomers (Ferris and Tang 1979).

The clinical utility of stereospecificity is unclear. Urine levels of the levo isomer have been used to measure compliance in amphetamine-addicted patients prescribed dextroamphetamine for maintenance or detoxification; the logic is that the more levo isomer present in urine, the less compliance (George and Braithwaite 2000).

Perhaps the most clinically useful difference between amphetamine isomers involves their differential effects on reinforcement. Studies in rats have shown that the dextro isomer is four times more potent than the levo isomer in promoting lever pressing for intracranial stimulation (Hunt and Atrens 1992). However, that pure dextroamphetamine is better for the treatment of ADHD than, for example, the mixed salts of dextroamphetamine/amphetamine is neither obvious nor conclusively shown. In addition, the overall greater potency of the dextro form for central actions suggests that this form may have a higher potential for abuse.

Pharmacological Profile

Amphetamines are noncatecholamine, sympathomimetic amines with CNS stimulant activity that causes catecholamine efflux and inhibits the reuptake of these neurotransmitters (see subsection "Mechanism of Action" later in this section).

Pharmacokinetics and Disposition

Amphetamine is highly lipid soluble and reaches peak levels in approximately 2 hours. Because of this lipid solubility, amphetamine has rapid distribution into tissues and transit across the blood-brain barrier. The protein binding is highly variable, but the average volume of distribution (V_d) is 5 L/kg.

The half-life of amphetamine is approximately 16-30 hours. On average, 30% of amphetamine is excreted unchanged.

Multiple extended-release preparations of both methylphenidate and amphetamine have been created to allow the drug to be taken only once a day. In addition, a delayed-onset preparation of methylphenidate allows the patient to take the drug in the evening but not have the onset of effect until the next day.

For patients, the Medication Guides issued with many prescribed drugs provide information about the available dosage forms, strengths, and markings (U.S. Food and Drug Administration 2023). These handouts are valuable for educating patients about proper use of drugs and potential side effects and can help reduce the risk of medication errors and severe adverse effects.

Mechanism of Action

The classic mechanism of action of amphetamine involves rapid diffusion directly into neuron terminals; through dopamine and norepinephrine transporters, amphetamine enters vesicles, causing release of dopamine and norepinephrine (Hutson *et al.* 2014). The release of these neurotransmitters into the synapse mediates some of the psychological and motoric effects of amphetamine, including euphoria, increased energy, and locomotor activation.

Side Effects and Toxicology

The side effects of amphetamines are predictable relative to their sympathomimetic pharmacology. The most common effects are nervousness, agitation, and decreased sleep. Serious adverse consequences have been observed with amphetamines and include arrhythmias, hyperpyrexia, rhabdomyolysis, and convulsions. Death, although uncommon, generally occurs only after the manifestation of one of these symptoms. Hallucinosis and psychosis are common complications of injected or inhaled amphetamines but are uncommon with oral intoxication.

Methamphetamine is more frequently associated with complications; because of its higher toxicity, it is not clear whether severe complications are dose dependent. For example, in a retrospective study of methamphetamine-related deaths in a large city, methamphetamine use was significantly associated with a higher risk of coronary artery disease, as well as a higher rate of subarachnoid hemorrhage, although it was of course impossible to determine whether the subjects were first-time users or chronic users (Karch *et al.* 1999). Of particular note in this study, blood levels of methamphetamine did not differ between the group in which methamphetamine was judged to be the cause of death and the group in which methamphetamine was detected but judged not to be related to the cause of death, suggesting that these toxicities are not necessarily dose dependent. Similarly, in one 5-year study, methamphetamine accounted for 43% of rhabdomyolysis cases in an emergency department setting.

Methamphetamine is more neurotoxic than amphetamine; it can cause destruction of dopaminergic neurons in the basal ganglia and thus is widely thought to increase the likelihood of future parkinsonism (Callaghan *et al.* 2012; Granado *et al.* 2013; Guilarte 2001). Although it is commonly believed that MDMA (3,4-methylenedioxy-*N*-methamphetamine, "ecstasy") is toxic primarily to serotonergic neurons (Sprague *et al.* 1998), evidence shows that it is also toxic to dopaminergic neurons (Simmler and Liechti 2018).

Seizures are fairly common in amphetamine misuse scenarios, especially with the more potent methamphetamine and hallucinogenic analogs.

Stimulant psychosis--often referred to as paranoid psychosis--is also common in amphetamine misuse scenarios because of the overwhelming presentation of the eponymous symptom (Chiang *et al.* 2019). Visual hallucinations are also disproportionately common with amphetamine psychosis. Psychosis is often seen together with stereotypy. In humans, stereotypy can take many forms but usually is expressed as pacing, searching, or examining minute details.

Drug-Drug Interactions

A comprehensive review found that drug interactions with amphetamine were mostly pharmacodynamic (Markowitz and Patrick 2001); however, because a small portion of amphetamine metabolism occurs via the cytochrome P450 (CYP) 2D6 isoenzyme, drugs that inhibit 2D6 metabolism can, theoretically, have the effect of increasing the plasma level of amphetamine.

Lisdexamfetamine

Lisdexamfetamine dimesylate, a prodrug that on absorption is metabolized to dextroamphetamine and L-lysine, was approved in 2007 for the treatment of ADHD and in 2014 was approved for the treatment of binge-eating disorder in adults. Food does not affect absorption of lisdexamfetamine, but acidification of the urine results in more rapid clearance.

Two small studies of children found good efficacy and tolerability for lisdexamfetamine in the treatment of ADHD. A 4-week randomized, double-blind, forced-dose, parallel-group study compared lisdexamfetamine 30, 50, or 70 mg/day with placebo in children (ages 6-12 years) with ADHD (Biederman *et al.* 2007b). Efficacy, as measured by scores on the ADHD Rating Scale-Version IV, the Conners Parent Rating Scale, and the Clinical Global Impression-Improvement (CGI-I) scale, was statistically superior to that of placebo for all dosages tested. A randomized, double-blind, placebo-controlled crossover study compared lisdexamfetamine with placebo and extended-release mixed amphetamine salts (Adderall XR) in 52 children (ages 6-12 years) with ADHD in an analog classroom setting (Biederman *et al.* 2007a). The study found comparable efficacy and safety for the active medications and superiority over placebo as measured by scores on the CGI-I scale and the Swanson, Kotkin, Agler, M-Flynn, and Pelham Deportment subscale. In a 4-week forced-dose (30, 50, or 70 mg/day) study of 420 adults with ADHD, lisdexamfetamine was found to have significantly greater efficacy over placebo as measured by ADHD Rating Scale scores. Human liability studies have also found lower abuse-related drug-liking scores compared with immediate-release D-amphetamine at equivalent dosages (Najib 2009).

The approval of lisdexamfetamine for binge-eating disorder was based on several large registration trials. The registration trials involved more than 700 patients with moderate to severe binge-eating disorder. In a Phase II trial, subjects were randomly assigned to 30, 50, or 70 mg/day lisdexamfetamine or placebo for 3 weeks and maintained at this dosage for an additional 8 weeks. Compared with placebo, the 50-mg/day and 70-mg/day dosages were more effective in reducing the total number of binge-eating days, were more likely to result in a remission of symptoms, and produced greater global improvement (McElroy *et al.* 2015a). Subsequent to that study, two Phase III trials have evaluated the efficacy and safety of lisdexamfetamine (target dosage of 50 or 70 mg/day as tolerated) versus placebo in adults ages 18-55 years with binge-eating disorder. Lisdexamfetamine at both dosages was more effective than placebo in reducing the total number of binge days. The active treatment groups showed a reduction in binge-eating days from an average of 5 days/week to 1 day/week (versus a reduction to about 2 days/week in the placebo group). Compared with subjects who received placebo, those who received active treatment experienced greater overall improvement, as measured by the CGI-I score (McElroy *et al.* 2016).

A number of preliminary studies suggested that lisdexamfetamine might be useful as an adjunctive treatment for major depressive disorder. Trivedi *et al.* (2013) found that 20-50 mg of lisdexamfetamine added to escitalopram for 6 weeks was superior to placebo in treating residual symptoms of depression. However, two subsequent Phase III randomized controlled trials failed to demonstrate a significant benefit for lisdexamfetamine over placebo in the adjunctive treatment of major depressive disorder (Corp *et al.* 2014; Giacobbe *et al.* 2018). Still, there is some evidence that lisdexamfetamine may be more effective than placebo in treating executive function deficits in patients with major depressive disorder (Madhoo *et al.* 2014) and that it may have a role in the treatment of bipolar depression (McElroy *et al.* 2015b).

Methylphenidate

Methylphenidate has FDA-approved indications for the treatment of ADHD and narcolepsy.

Structure-Activity Relations

Although methylphenidate has two chiral centers, only one contributes to its clinical effect. The D- and L-threo enantiomers are in a racemic mixture, although a single-isomer form of methylphenidate, dexmethylphenidate [*(R,R)*-(+)], is currently being marketed under the brand name Focalin.

There are some differences in the pharmacological parameters of the two isomers, as described in the following subsection (Mariotti *et al.* 2013).

Pharmacokinetics and Disposition

Methylphenidate is almost totally absorbed on oral administration (as is the single isomer dexmethylphenidate), although it is absorbed at a faster rate in the presence of food than without food (Chan *et al.* 1983). Methylphenidate has low protein binding (15%) and is fairly short acting; the effects last approximately 4 hours, with a half-life of 3 hours. The primary means of clearance is through the urine, in which 90% is excreted.

Mechanism of Action

Although it is both a norepinephrine and a dopamine reuptake inhibitor, methylphenidate appears to exert its effects primarily through its action on dopamine neurobiology. It blocks the dopamine transporter and increases extracellular dopamine (Mariotti *et al.* 2013). The amount of extracellular dopamine increase varies greatly among individuals, depending on the extent of both dopamine transporter blockade and baseline dopamine release.

Side Effects and Toxicology

The common side effects of methylphenidate are similar to those of amphetamine and include nervousness, insomnia, and anorexia, as well as dose-related systemic effects such as increased heart rate and blood pressure. Overdose may lead to seizures, dysrhythmias, or hyperthermia (Klein-Schwartz 2002). At therapeutic dosages, discontinuation symptoms tend to be slight, but with chronic use, symptoms similar to those in amphetamine withdrawal, including lethargy, depression, and paranoia, can occur (Klein-Schwartz 2002).

Drug-Drug Interactions

Although theoretically a substrate of CYP2D6, methylphenidate was found not to have any significant metabolism in humans via this enzyme (DeVane *et al.* 2000). The prescribing information (Novartis 2021) does cite methylphenidate's potential ability to inhibit the metabolism of warfarin, some antiepileptic agents, and tricyclic antidepressants (TCAs), and therefore caution should be observed. However, a review found that methylphenidate is safe and has minimal drug-drug interactions, with the exception of concomitant MAOI use (Markowitz and Patrick 2001).

Modafinil

Modafinil was the first FDA-designated "wakefulness-promoting agent"; it is approved by the FDA for the treatment of excessive sleepiness associated with narcolepsy, sleep apnea, and residual sleepiness after standard treatment for shift-work sleep disorder (SWSD) (Cephalon Inc. 2008). As described below, modafinil does little to prevent or alter sleep when one is trying to do so; however, it appears to permit more stable wakefulness (i.e., reduced sleep propensity) when one is attempting to stay awake in the presence of elevated sleep pressure.

Structure-Activity Relations

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) exists in racemic form. Both stereoisomers appear to have the same activity in animals.

Pharmacokinetics and Disposition

Modafinil, the primary metabolite of adrafinil, lacks many of the side effects found in adrafinil, such as increased liver enzymes, anxiety, and stomach pain. Modafinil is rapidly absorbed but slowly cleared. It has fairly high protein binding (60%) and a V_d of 0.8 L/kg. Its half-life is 11-14 hours.

The metabolism of modafinil is complex. In contrast to excretion of amphetamines, less than 10% of modafinil is excreted unchanged.

Metabolism is primarily via CYP3A4/5. It has been reported that modafinil also has in vitro capacity to induce CYP3A4 (Robertson *et al.* 2000), especially gastrointestinal 3A4. A clinically significant reduction of triazolam has been reported (Robertson *et al.* 2002).

Mechanism of Action

The precise mechanism by which modafinil exerts its wakefulness-promoting effect in patients with excessive sleepiness due to narcolepsy is not yet known. Not surprisingly, given its efficacy in narcolepsy, modafinil is not observed to increase c-Fos activity in hypocretin cells, as well as in the tuberomammillary nucleus (which is primarily histaminergic), striatum, and cingulate cortex at higher dosages (Scammell *et al.* 2000). Additionally, in rats, an increase in histamine release in the anterior hypothalamus is seen (Ishizuka *et al.* 2003). However, modafinil's wakefulness-promoting effects were not decreased in histamine knockout mice (Bonaventure *et al.* 2007).

What may be an important aspect of the pharmacology of modafinil is its lack of effect on the neuroendocrine system. A comparison of healthy volunteers who were sleep deprived for 36 hours without modafinil with those who received modafinil during sleep deprivation found no difference in cortisol, melatonin, or growth hormone levels (Brun *et al.* 1998).

Side Effects and Toxicology

Modafinil appears to be well tolerated, with the most common side effects being headache and nausea. Side effects have been found to increase with dosages from 100 to 600 mg/day, and very high dosages (800 mg/day) have been found to be associated with higher rates of tachycardia and hypertension (Wong *et al.* 1999). Overall, only 5% of the patients in Phase III trials discontinued modafinil because of side effects (Cephalon Inc. 2008).

Modafinil appears to be fairly safe at high dosages. Reports indicate that 32 patients have safely taken 1,000 mg/day for more than 50 days; one patient safely took 1,200 mg/day for 21 consecutive days. Two patients took 4,000 mg and 4,500 mg, respectively, in a single dose and experienced only transient (< 24 hours) agitation and insomnia with mild elevations in heart rate and blood pressure (Cephalon Inc. 2008). There have been no reports of seizures with modafinil.

During the attempts to obtain FDA approval of modafinil for the treatment of ADHD, concerns arose over the possibility that modafinil may carry a risk of Stevens-Johnson syndrome. Three cases of drug-induced rash were reported during clinical trials (U.S. Food and Drug Administration 2007).

The package insert notes a risk of "serious rash, including Stevens-Johnson syndrome," in adults and children and cautions that modafinil is not indicated for children. The insert cites a rash incidence of 0.8% in pediatric patients, with one case of possible Stevens-Johnson syndrome and one case of multiorgan hypersensitivity reported, and concludes with the statement that although there are no known predictive factors, benign rashes do occur, and modafinil should be discontinued if rash develops.

Drug-Drug Interactions

As described earlier in this section, modafinil induces CYP3A4/5 and thus conceivably could lower the plasma concentrations of medications with substantial 3A4/5 metabolism. However, it is not clear whether this induction is substantial only on the gastrointestinal cytochrome and is thus relevant only for other drugs undergoing significant first-pass metabolism (Darwish *et al.* 2010).

Modafinil inhibits CYP2C19 in vitro (Robertson *et al.* 2000). It is prudent to assume that the effect of modafinil on the cytochrome system is not well characterized and to be vigilant for these potential drug-drug interactions.

Armodafinil

Armodafinil (l-*[R]*-modafinil or [[?]]-*[R]*-modafinil) is the longer-acting isomer of racemic modafinil. In 2007, armodafinil received FDA approval for the same indications as modafinil, specifically excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS) as an adjunct to standard treatment, and SWSD.

Armodafinil and racemic modafinil produce comparable peak plasma concentrations, although the peak for armodafinil occurs later than that for modafinil and is maintained for 6-14 hours postdose (Dinges *et al.* 2006).

Armodafinil has been studied in multiple randomized controlled trials in the treatment of sleep disorders. For example, two early 12-week double-blind studies using armodafinil 150 mg as an adjunct to continuous positive airway pressure (CPAP), both in patients who were otherwise stable except for some residual sleepiness (Hirshkowitz *et al.* 2007) and in patients who were still symptomatic (Roth *et al.* 2006), found improvements in wakefulness measures. Armodafinil also significantly improved the quality of episodic secondary memory (i.e., the ability to recall unrehearsed information). Whether this effect was due directly to the medication, to improved wakefulness, or to decreased hypoxia (as a function of being more awake) is unclear. However, armodafinil did not adversely affect the CPAP or any other physiological parameters.

A 12-week double-blind study of armodafinil in narcolepsy found improvements similar to those seen with modafinil. These included improved wakefulness (as measured by the Maintenance of Wakefulness Test), improved Clinical Global Impression of Change (CGI-C) scores, and improvement in memory and attention. Armodafinil 150 mg/day and 250 mg/day were similarly effective (Harsh *et al.* 2006).

In SWSD, armodafinil 150 mg/day was tested against placebo in a 12-week study, showing significant prolongation of time to sleep onset and an improvement in overall clinical condition based on CGI-C scores. Armodafinil had no effect on daytime sleep polysomnography (Roth *et al.* 2005).

Daytime sleepiness has been implicated in an increased risk of motor vehicle accidents in patients with obstructive sleep apnea. Armodafinil has demonstrated efficacy for patients with obstructive sleep apnea in improving alertness in driving simulations without affecting compliance on CPAP (Kay and Feldman 2013).

Clinical Uses of Stimulants and Wakefulness-Promoting Agents

Although stimulants have been used for many years in a number of clinical scenarios, double-blind, randomized controlled trials examining their safety, efficacy, and effectiveness in neurobehavioral disorders other than ADHD are rare. Most of the support for their use comes from open-label studies and case series. Randomized trials of modafinil for neurobehavioral disorders with symptoms of sleepiness and fatigue are beginning to be published.

Attention-Deficit/Hyperactivity Disorder

Multiple double-blind, placebo-controlled studies have shown the efficacy of stimulants for ADHD, and their use is well investigated in both adults and children (Greenhill *et al.* 2002; Wilens *et al.* 2002). Some studies are aimed at showing the superiority of one preparation relative to another, although this approach is not always fruitful; for example, one study comparing various single-dose amphetamine preparations with one another and with placebo over 8 weeks found that they were all superior to placebo (James *et al.* 2001). However, immediate-release amphetamines had a faster onset but shorter duration of action; spansules, although much slower to take effect than the others, lasted several hours longer.

With respect to individual stimulants, all appear to be equally efficacious in the treatment of ADHD, but they have been reported to have different time courses. In a double-blind, double-control (placebo and methylphenidate) study, the mixed amphetamine salts of Adderall were found to exert their effects rapidly but to dissipate quickly over the course of the day, although Adderall lasted longer than methylphenidate (Swanson *et al.* 1998). Notably, higher doses of Adderall lasted longer than lower doses, indicating a dose-dependent effect in duration of action not found with methylphenidate. Thus, although stimulants may appear to be of equal efficacy overall, there is considerable variability in individual response to each stimulant.

The decision to choose amphetamines or methylphenidate for the treatment of ADHD is often based on the clinician's preference and degree of experience with the medication. At least one important blinded crossover study found that in performance tasks, the two drugs were generally equally efficacious (Efron *et al.* 1997).

Modafinil is not FDA approved for the treatment of ADHD but has shown some efficacy in clinical trials. A 4-week double-blind study with an 8-week open-label extension found modafinil to be efficacious across all ADHD rating subscales for the duration of the open-label extension (Boellner *et al.* 2006). Interestingly, 10% of the 220 children studied lost an average of 3 kg, while 4% gained the same amount. Another such double-blind study found significant efficacy with a dosage of 300 mg/day, although heavier children ([?] 30 kg) needed 400 mg/day (Biederman *et al.* 2006). A pooled analysis of three trials (638 patients) found that modafinil produced similarly greater and impressive improvements in ADHD rating scale scores for both stimulant-naive and prior-stimulant subgroups relative to placebo (Wigal *et al.* 2006). As in other studies, insomnia and headache were the most common side effects but were infrequent overall. A 9-week trial (Biederman *et al.* 2005) found that almost half of patients (mean age 10 years, mean dosage 368 mg/day) were much or very much improved, and efficacy was seen in both inattentive and hyperactive subgroups and both school and home ratings. Some small but controlled trials (Rugino and Samsock 2003; Turner *et al.* 2004) found efficacy with modafinil, and in one study (Taylor and Russo 2000), equivalence to dextroamphetamine was shown. Modafinil is currently indicated only for the treatment of excessive sleepiness associated with narcolepsy, OSAHS, and SWSD.

Stroke and Traumatic Brain Injury

The results of studies on the effects of stimulants on patients who had strokes or traumatic brain injury are mixed. Although small early studies showed some superiority of amphetamine to placebo in improving motor function poststroke (Crisostomo *et al.* 1988; Walker-Batson *et al.* 1995), subsequent, more carefully controlled studies of amphetamine in geriatric stroke patients did not show superiority to placebo in improving motor function (Goldstein *et al.* 2018; Sonde *et al.* 2001). Neither was amphetamine found to be superior to placebo in improving somatosensory training outcomes (Knecht *et al.* 2001). Modafinil also has not been consistently effective in the treatment of fatigue associated with traumatic brain injury (Jha *et al.* 2008). In contrast, relative to placebo, dextroamphetamine 10 mg/day significantly improved language recovery in poststroke aphasic patients when immediately coupled with a session of speech therapy; this effect was seen as quickly as within 1 week (Walker-Batson *et al.* 2001). A review lamented the lack of good data in brain-injured patients but did note that available data suggest that the bulk of stimulant efficacy may lie with its improvements in mood and cognitive processing (Whyte *et al.* 2002).

Although there is a dearth of placebo-controlled studies, there are some interesting reports in which stimulants were compared with antidepressants for patients with poststroke depression. One such study, comparing methylphenidate with TCAs, found similar and significant response to both drugs, although the stimulant worked faster (Lazarus *et al.* 1994).

Modafinil has been reported to have therapeutic efficacy in some types of brain injury. Two double-blind studies by the same group (Saletu *et al.* 1990, 1993) found modafinil effective in improving cognition and accelerating improvement in attention and concentration for patients with alcoholic brain syndrome. Similarly, Joos *et al.* (2013) found that 10 weeks of modafinil treatment significantly improved working and verbal memory for patients with DSM-IV-defined alcohol dependence. In addition, there is some evidence that modafinil may help with cognition for patients with traumatic brain injury (Dougall *et al.* 2015; Maksimowski and Tampi 2016).

Cocaine and Stimulant Use Disorders

It may not be surprising that a double-blind study showed sustained-release dextroamphetamine to be superior to placebo in reducing cocaine use (Grabowski *et al.* 2001). However, similarly designed studies by the same authors did not find this effect with methylphenidate (Grabowski *et al.* 1997) or with risperidone (Grabowski *et al.* 2000). A double-blind, placebo-controlled study found that modafinil did not increase the euphoria or craving for cocaine; in fact, it may have blunted the euphoria (Dackis *et al.* 2003). A double-blind, placebo-controlled study of 62 patients found that modafinil-treated patients had a longer duration of cocaine abstinence (> 3 weeks), with no dropouts due to adverse events (Dackis *et al.* 2005). Likewise, a 48-day double-blind trial found that under controlled laboratory conditions, modafinil significantly attenuated self-administration and effects of cocaine (Hart *et al.* 2008). However, a large randomized controlled study of modafinil in the treatment of 210 subjects with DSM-IV-TR (American Psychiatric Association 2000)-defined cocaine dependence did not find modafinil generally efficacious in improving abstinence from cocaine use (Dackis *et al.* 2012), although there was a trend for male patients receiving a modafinil dosage of 400 mg/day to be less likely to use cocaine. More study is needed to determine which, if any, patients with cocaine dependence might benefit from modafinil treatment.

Alcohol Use Disorder

Basic research suggests that amphetamine appears to have an unexpected effect in alcohol use disorder. In rats, amphetamines reduced alcohol consumption during choice trials; this reduction was specific to alcohol intake, because amphetamine administration had no effect on rodents' intake of water (Yu *et al.* 1997). This effect of amphetamine on alcohol consumption may involve the neurobiology of reward systems (Ellison and Potthoff 1987). Much more research is needed to identify the mechanisms by which stimulants affect alcohol intake.

Narcolepsy

Stimulants have traditionally been used to treat excessive sleepiness associated with narcolepsy. Narcolepsy is characterized by excessive sleepiness that is typically associated with cataplexy and other REM sleep phenomena such as sleep paralysis and hypnagogic hallucinations. Modafinil's approval for treatment of excessive sleepiness in narcolepsy was based on substantial evidence from large multicenter clinical trials (Broughton *et al.* 1997; U.S. Modafinil in Narcolepsy Multicenter Study Group 1998, 2000). Modafinil is less disruptive of sleep than amphetamines and is thought to have a lower abuse potential (Shelton *et al.* 1995) (see Table 45-1). One study found that taking an extra dose (200 mg) at midday improved wakefulness in patients with narcolepsy without causing insomnia at night (Schwartz *et al.* 2004). Importantly, cataplexy--the sudden occurrence of muscle weakness in association with experiencing laughter, anger, or surprise--is responsive to amphetamines but not to modafinil ("Modafinil" 1999; Shelton *et al.* 1995).

Fatigue

The use of stimulants to treat fatigue syndromes may seem intuitive, but evidence from large-scale controlled clinical trials to support this use is mixed. In one of the

only double-blind, placebo-controlled studies, men with HIV, depression, and fatigue had significantly less fatigue with dextroamphetamine (73% response [Wagner and Rabkin 2000]). Tolerance, dependence, and misuse were not observed, even across a 6-month open phase. A double-blind study of methylphenidate and pemoline in a similar group of 144 patients with HIV who had severe fatigue found both stimulants effective in improving fatigue and quality of life (Breitbart *et al.* 2001). Rabkin *et al.* (2011) found that a significant majority of HIV patients--including those with comorbid hepatitis C--reported an improvement in fatigue with armodafinil.

As with HIV, cancer-related fatigue (CRF) is strongly correlated with a negative quality of life (Curt *et al.* 2000). Stimulants have long been prescribed for CRF. In one of the larger trials of stimulants (or stimulant-like agents) in the treatment 631 patients with CRF, Jean-Pierre *et al.* (2010) found that modafinil was more effective than placebo in helping patients with severe fatigue. However, modafinil did not separate from placebo in patients with cancer and mild or moderate fatigue at baseline. Similarly, in a Phase III study of armodafinil 150 mg/day for 8 weeks in the treatment of CRF in patients with multiple myeloma, armodafinil failed to separate from placebo (Berenson *et al.* 2015). In addition, no advantage was found for armodafinil in a controlled study of the treatment of brain radiation-related fatigue (Page *et al.* 2015). On the other hand, 10 mg of methylphenidate was significantly more effective than placebo in treating CRF in 38 patients with advanced cancer who were undergoing palliative care in Denmark (Pedersen *et al.* 2020).

Two controlled trials (Adler *et al.* 2003; Hogl *et al.* 2002) found modafinil effective in reducing excessive sleepiness in patients with Parkinson's disease. Findings from open-label studies of modafinil for fatigue in multiple sclerosis (Rammohan *et al.* 2002) and myotonic dystrophy (Damian *et al.* 2001) suggest modafinil's utility in management of fatigue. However, a carefully controlled study of methylphenidate, modafinil, and amantadine in the treatment of fatigue in patients with multiple sclerosis found that none of these agents separated from placebo (Nourbakhsh *et al.* 2021). A small double-blind crossover study of modafinil in myotonic dystrophy found a reduction in fatigue but no improvement on activity measures (Wintzen *et al.* 2007). This result would be consistent with modafinil's selective effect on wakefulness and minimal impact on motor or autonomic parameters. In the same vein, studies of modafinil for patients with fibromyalgia (Schwartz *et al.* 2007) and of armodafinil for patients with sarcoidosis (Lower *et al.* 2013) did find that the medications were useful in treating the fatigue associated with these disorders.

Obstructive Sleep Apnea/Hypopnea Syndrome

There are multiple placebo-controlled studies of modafinil in the treatment of residual sleepiness in patients with DSM-IV-TR-defined obstructive sleep apnea (Chapman *et al.* 2016; Greenblatt and Adams 2021; Kingshott *et al.* 2001; Pack *et al.* 2001). These studies show modafinil's efficacy in treating the residual daytime sleepiness experienced by some patients with OSAHS who were compliant in their use of CPAP treatment.

Importantly, modafinil's use was studied in--and should be limited to--the treatment of excessive sleepiness associated with OSAHS only after CPAP has been instituted and optimized. OSAHS carries significant cardiovascular risks if the airway collapse during sleep is not treated appropriately with CPAP and related therapies. It is conceivable that lessened daytime sleepiness from use of modafinil might fool the patient into thinking that CPAP is unnecessary, thus posing a risk via the untreated underlying OSAHS.

Obesity and Binge-Eating Disorder

That amphetamines are anorectic is well known; however, the extent of the effect may be overstated. Bray and Greenway (1999) summarized the studies of obesity treatments, wherein they cited a large review of more than 200 short-term (3-month) double-blind studies of various noradrenergic agents, including amphetamine and amphetamine derivatives. Individuals taking stimulants were twice as likely as those taking placebo to lose 1 lb/week; however, the percentage of those who lost 3 lb/week was quite low (10%). A small study found that high dosages of amphetamine (30 mg/70 kg daily) decreased overall caloric intake but did so primarily through a decrease in fat consumption; carbohydrate consumption actually increased (Foltin *et al.* 1995). This mild effect on appetite is important when considering the use of stimulants by older adults who lack both energy and motivation and have a poor appetite.

The efficacy of stimulants in treating binge-eating disorder has been demonstrated in multiple studies of lisdexamfetamine. As reported earlier, Phase III randomized controlled trials demonstrate significant efficacy for lisdexamfetamine in decreasing binge-eating episodes and OCD features associated with binge eating (McElroy *et al.* 2016). Furthermore, lisdexamfetamine treatment of binge eating over a 6-month period appears to significantly reduce the risk of relapse (Hudson *et al.* 2017), and the beneficial effects of the drug on binge eating are often seen as early as the first week of treatment (McElroy *et al.* 2017).

Depression

As described earlier in this chapter, the only large-scale randomized controlled studies of a stimulant in the treatment of depression have involved lisdexamfetamine. Whereas early controlled studies suggested a benefit from adjunctive lisdexamfetamine (Trivedi *et al.* 2013) in the treatment of depression, subsequent Phase III trials failed to demonstrate the efficacy of lisdexamfetamine in the treatment of residual depressive symptoms after selective serotonin reuptake inhibitor (SSRI) treatment (Richards *et al.* 2016).

Beyond the lisdexamfetamine data, the bulk of the evidence for the utility of stimulants in the treatment of depression derives from case series by Feighner *et al.* (1985) and Fawcett *et al.* (1991), which suggested the efficacy of stimulants combined with MAOIs and MAOI/TCA combinations as well as their safety in not causing hypertensive or hyperthermic crises, and case series by Stoll *et al.* (1996) and Metz and Shader (1991), in which a combination of a stimulant and an SSRI was used. Another case series argued for amphetamine's ability to augment an antidepressant effect for patients with only partial response to their current medication; not unexpectedly, the effects were primarily in improving fatigue and apathy (Masand *et al.* 1998).

In an open-label trial of depressed patients with cancer, both amphetamine and methylphenidate were reported to improve depressive symptoms to the same extent, and effects were seen within 2 days. In this series, stimulants did not cause anorexia; in fact, they improved appetite in more than half of the patients studied (Olin and Masand 1996), suggesting that these agents are not contraindicated solely on the basis of concerns about anorexia. However, a more carefully controlled, double-blind study of 77 patients with advanced-stage cancer found no benefit of methylphenidate over placebo in treating depressive symptoms (Centeno *et al.* 2022).

In a review, Orr and Taylor (2007) noted the paucity of high-quality data and suggested a possible role for stimulants in depression, particularly as adjunctive agents, in specific patient subgroups.

The utility of modafinil in depressive states has been examined in a number of open-label and controlled studies. For example, the mood-altering properties of modafinil were studied in 32 healthy volunteers in a double-blind crossover inpatient study (Taneja *et al.* 2007). Modafinil had positive results on general mood, especially on alertness and energy measures, but also had a negative effect on calmness (i.e., increased anxiety).

A double-blind, placebo-controlled trial (Dunlop *et al.* 2007) examining the effects of modafinil initiated at the outset of treatment with an SSRI in depressed patients with fatigue found no difference in the primary outcome measure of the Epworth Sleepiness Scale but found some improvement on the hypersomnia items of the 31-item Hamilton Rating Scale for Depression. Two other controlled trials (DeBattista *et al.* 2003; Fava *et al.* 2005) and two open-label trials (DeBattista *et al.* 2001; Menza *et al.* 2000) suggest that modafinil may have some utility as an augmentation agent to antidepressants for depressed patients with fatigue or excessive sleepiness.

Both modafinil and armodafinil have shown some preliminary benefit in the treatment of bipolar depression. Frye *et al.* (2007) found that the addition of modafinil at dosages of 100-200 mg/day to a standard mood stabilizer for 6 weeks was more effective than the addition of placebo for 85 patients with bipolar depression. In a larger randomized controlled multicenter study (Calabrese *et al.* 2010), 257 patients with bipolar depression taking either lithium or valproate were randomly assigned to receive augmentation treatment with 150 mg/day armodafinil or placebo. Armodafinil appeared to help some--but not all--patients with bipolar depression, and the differences between groups did not reach statistical significance. Likewise, a study of 399 bipolar depressed patients randomly assigned to receive adjunctive armodafinil or placebo for 8 weeks failed to demonstrate armodafinil's benefit on the primary outcome measure (mean change from baseline on the 30-Item Inventory of Depressive Symptomatology-Clinician-Rated [IDS-C30] total score [Frye *et al.* 2015]). However, armodafinil was efficacious on a number of secondary measures, including IDS-C30 remission and Global Assessment of Functioning scores.

Negative Symptoms and Cognitive Deficits in Schizophrenia

Whereas positive symptoms of schizophrenia are often responsive to antipsychotics, negative symptoms and cognitive deficits are often not (Tandon 2011). Because the negative symptoms and cognitive impairments of schizophrenia are often more disabling than the positive symptoms, there has been interest in developing effective treatments for these symptoms and deficits. A number of studies have explored the efficacy of modafinil and armodafinil in the treatment of negative symptoms and cognitive deficits in schizophrenia, with mixed results. For example, whereas some studies

have found that modafinil and armodafinil improve negative symptoms (Arbabi *et al.* 2012; Kane *et al.* 2010) and working memory (Scoriels *et al.* 2012) for some schizophrenic patients, other studies have found no benefit (Bobo *et al.* 2011; Pierre *et al.* 2007; Sevy *et al.* 2005). A meta-analysis of all studies to date concluded that the benefits of modafinil and armodafinil are modest at best (Andrade *et al.* 2015). Despite these mixed results, modafinil has been well tolerated in most studies of schizophrenia. By contrast, stimulants such as dextroamphetamine may worsen positive symptoms of schizophrenia and have been less commonly studied in the treatment of negative symptoms and cognitive impairments. Further study is needed to determine the role of stimulants and wakefulness-promoting agents in schizophrenia.

Conclusion

The safety and efficacy of stimulants for the treatment of ADHD have been well established. Modafinil and armodafinil are also firmly established as efficacious wakefulness-promoting agents in narcolepsy, sleep apnea, and SWSD. The utility of these drugs in other areas is being examined. Although there is intense interest in the potential use of stimulants and modafinil in other psychiatric and neurobehavioral conditions, controlled studies of their safety and efficacy are limited, and results have been mixed. It is unclear why stimulants have not been extensively investigated for clinical utility for indications other than the treatment of ADHD. The approval of armodafinil, as the newest of the wakefulness-promoting compounds, may spur further research. Well-designed large-scale controlled trials are needed to define and characterize the role of stimulants and modafinil in various psychiatric illnesses. It is hoped that this will be an area of continued interest and development, from the elucidation of the molecular mechanisms of stimulants and modafinil/armodafinil to the demonstration, through controlled trials, of their potential clinical safety and benefits.

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CHAPTER 46

Electroconvulsive Therapy and Other Neuromodulation Therapies

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Electroconvulsive therapy (ECT) has proven to be one of the most effective somatic treatments for mood disorders (Kellner *et al.* 2012). ECT research has focused on techniques to maximize the efficacy of ECT and minimize side effects and to elucidate ECT's mechanism of action. In this chapter, the history of ECT is reviewed as well as the preclinical and clinical data on the mechanism of action of ECT and the relevant literature related to the efficacy and side-effect burden of ECT. Practical guidelines for the administration of ECT are outlined, including the efficacy of ECT in treating various psychiatric disorders, appropriate patient selection, stimulus settings and electrode placement, pretreatment medical evaluation, and management of the patient during acute, continuation, and maintenance courses of ECT. Finally, recent developments with investigative convulsive neuromodulation methods--individualized low-amplitude seizure therapy (iLAST), investigational magnetic seizure therapy (MST), and focal electrically administered seizure therapy (FEAST)--will be discussed.

History of Electroconvulsive Therapy

The development of ECT occurred at a time when few somatic treatments were available for psychiatric disorders and physicians were struggling to find treatments for severely ill psychotic patients. In 1935, Manfred Sakel induced hypoglycemic coma (i.e., insulin shock therapy) as a treatment for psychiatric patients, and in the same year Laszlo Meduna injected patients with pentylenetetrazol to induce convulsions in order to treat psychosis. Three years later, Italian psychiatrists Ugo Cerletti and Lucio Bini used electricity to induce seizures. Electroshock treatment proved safer and easier to administer than chemically induced seizures and replaced other methods of inducing seizures.

Modern psychopharmacology developed with the discovery of lithium (1949) and iproniazid (1957) for the treatment of mood disorders and the synthesis of the first antipsychotic, chlorpromazine (1952); the first tricyclic antidepressant, imipramine (1959); and the first benzodiazepine, chlordiazepoxide (1960). The development of psychotropic medications was associated with a decline in the use of ECT from the 1960s to the 1980s.

In the 1980s, the use of ECT began to increase in the United States (Thompson *et al.* 1994); however, the percentage of U.S. hospitals providing ECT declined by 43% from 1993 to 2009 (Case *et al.* 2013). ECT use in the United States is more common among older adults and white individuals (Luccarelli *et al.* 2020). Studies in Canada and Denmark demonstrated relatively stable rates of ECT utilization (Hundrup *et al.* 2017; Rapoport *et al.* 2006), whereas decreasing rates of ECT use have been reported in the United Kingdom and Australia (Plakiotis *et al.* 2012; Scott 2012). A metaanalysis of 18 international studies indicated declining global rates of ECT utilization from 1973 to 2013 (Lesage *et al.* 2016). By contrast, rates of ECT use have risen in China since 2014 and in the Netherlands from 2008 to 2015 (Ma *et al.* 2019; Verwey *et al.* 2017).

During this same period the results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush *et al.* 2009) demonstrated the limited effectiveness of psychopharmacology for major depressive disorder (MDD) and supported the continued clinical relevance of ECT for patients who do not respond to medication management (Insel and Wang 2009; McCall 2007).

Since the 1980s, the safety of ECT has increased significantly with the introduction of sophisticated cardiopulmonary and electroencephalographic monitoring, better anesthetic agents, and the adoption of the brief-pulse stimulus machine. Today, ECT is arguably the fastest, most effective treatment for mood disorders. ECT is also one of the safest procedures performed under general anesthesia, with a mortality rate reported at 0.002% or less (Torring *et al.* 2017; Watts *et al.* 2011).

As with so many aspects of health care, the COVID-19 pandemic has created complications in ECT administration and associated declines in utilization rates globally. This probably relates to common recipients of ECT (older adults) being particularly at risk from COVID-19, the need for health care resources (including providers and personal protective equipment) to be shifted to care for those with COVID-19, and the increased viral transmission risk inherent in ECT (e.g., airway management, inability to socially distance) relative to other psychiatric care options (Lapid *et al.* 2020; Sienaert *et al.* 2020).

Mechanism of Action of Electroconvulsive Therapy

Despite the use of ECT in psychiatry for more than 80 years and extensive preclinical and clinical studies, the mechanisms underlying ECT remain poorly understood. The lack of mechanistic understanding is not unexpected given the multitude of changes induced by electrical stimulation and generalized seizures and the lack of understanding of the biology of major psychiatric illnesses. Here we focus on several hypotheses about the actions of ECT.

Anticonvulsant Hypothesis

Because a course of ECT has anticonvulsant effects, it is possible that its therapeutic benefits result from changes in neural excitability. This hypothesis is based on observations that a course of ECT results in increases in seizure threshold and decreases in seizure duration (Sackeim 1999), and the hypothesis focuses on changes in neurotransmitters and biochemical processes regulating neural excitability. GABA is the major inhibitory transmitter in the brain and a target for multiple anticonvulsant drugs, some of which are used to treat psychiatric disorders. Data from animal studies indicate increases in the threshold for bicuculline-and pentylenetetrazol-induced seizures following a series of electroconvulsive shock (ECS) treatments (Nutt *et al.* 1981; Plaznik *et al.* 1989). Because bicuculline and pentylenetetrazol inhibit $GABA_A$ receptors, these findings suggest that ECT alters GABAergic inhibition. Additionally, GABA levels increase in certain brain regions after ECS (Green *et al.* 1982), and evidence from magnetic resonance spectroscopy indicates that ECT increases GABA levels in the occipital cortex in humans (Sanacora *et al.* 2003). Changes in GABA levels suggest that there may be an increase in tonic inhibition after repeated seizures, and effects on GABA-mediated tonic inhibition are increasingly recognized as an important mechanism of several neuroactive drugs, including the novel neurosteroid antidepressant brexanolone (Farrant and Nusser 2005; Meltzer-Brody *et al.* 2018). In line with this research is the finding that increased frontal delta activity (i.e., postictal depression) may be a marker for ECT response (Azuma *et al.* 2007; Mayur 2006) and is associated with decreased cerebral blood flow in the immediate postictal period (Nobler *et al.* 1993).

Similarities to Antidepressant Medications

Numerous studies have examined whether there are common mechanisms between ECT and clinically used antidepressant medications. ECT, akin to antidepressants, normalizes changes in the hypothalamic-pituitary-adrenal axis associated with MDD (Yuuki *et al.* 2005). ECT also has significant effects on biogenic amines, including norepinephrine, serotonin, and dopamine, major targets for antidepressant medications. Certain antidepressants cause a_1-adrenergic receptor subsensitivity, and similar effects are observed with ECS (Nutt and Glue 1993). ECS has multiple other effects on the adrenergic system, including increased norepinephrine turnover and possibly decreased presynaptic a_2-adrenergic receptor sensitivity. ECS also alters the serotonin system, producing increased behavioral responses to serotonin agonists and altered 5-hydroxytryptamine type 2 (5-HT$_2$) receptor binding in the cerebral cortex (Fochtmann 1994; Nutt and Glue 1993; Sackeim 1994). Thus, 5-HT$_2$ receptor downregulation, like a-adrenergic receptor subsensitivity, may be a mechanism common to several antidepressant treatments.

Accumulating evidence suggests that depression and other psychiatric illnesses involve neuroinflammatory changes. While ECT is a stressor that can elevate inflammatory markers acutely, some evidence indicates that over a course of treatment, ECT causes the levels of certain cytokines, including tumor necrosis factor-a and interleukin-5 and -6, to be reduced, which may contribute to beneficial effects (Jiang *et al.* 2017; Yrondi *et al.* 2018).

Neuroplastic Effects of Electroconvulsive Therapy

An intriguing avenue for elucidating the effects of ECT is to determine how ECT alters the neurocircuitry of mood regulation and depression. This circuitry involves connections between and within regions of the prefrontal cortex, anterior cingulate gyrus, subgenual prefrontal cortex, anterior thalamus, and more traditional limbic structures (hippocampus and amygdala) (Drevets 2000; Seminowicz *et al.* 2004). Multiple studies have documented structural changes including cell loss (glia and possibly neurons) and diminished neuropil in several of these regions in subtypes of depression (Harrison 2002). Several studies have found that ECT increases regional brain volumes in specific areas, particularly in the hippocampus and amygdala (Gyger *et al.* 2021; Takamiya *et al.* 2018), but it is unclear whether these apparent neuroplastic effects contribute to treatment efficacy (Oltedal *et al.* 2018) or whether they are specific for depression (Thomann *et al.* 2017).

It also appears that different antidepressant treatments differentially affect metabolism in mood circuitry. Effective treatment with paroxetine increases metabolism in frontal regions while decreasing metabolism in the hippocampus, whereas cognitive-behavioral therapy results in the opposite effects (Goldapple *et al.* 2004; Seminowicz *et al.* 2004). In contrast, ECT diminishes metabolism in the prefrontal cortex and hippocampus (Nobler *et al.* 2001). Studies using functional connectivity neuroimaging indicate that ECT dampens hyperconnected neural circuits in the prefrontal cortex (Perrin *et al.* 2012) and alters network coherence in the default mode network, a brain circuit involved in self-referential thinking (Mulders *et al.* 2016); these latter effects correlate with treatment response. A major challenge in interpreting existing functional connectivity neuroimaging studies is that these studies have largely relied on analysis of group data rather than individual connectomes (Gratton *et al.* 2020). A recent study using individual connectome imaging methods indicates that ECT-induced impairments in verbal memory reflect widespread changes in connectivity between networks that include the default mode network, the frontoparietal control network, and the hippocampus, changes that were not observed in group data (Wang *et al.* 2020). However, the same type of individual-level analysis did not find correlates of mood improvement, suggesting that therapeutic effects may be heterogeneous across individuals. Results from this latter study are consistent with an emerging hypothesis that certain psychiatric treatments, probably including ECT, promote homeostatic synaptic plasticity (synaptic scaling) as a way of modulating neural circuits (Kavalali and Monteggia 2020).

Several antidepressant treatments, probably including ECT, have neurotrophic effects and result in neurogenesis in the dentate gyrus of adult rodents (Madsen *et al.* 2000; Malberg *et al.* 2000; Scott *et al.* 2000), an area that also shows increased volume in humans after ECT (Takamiya *et al.* 2019). These effects may involve changes in brain-derived neurotrophic factor and its receptor tyrosine kinase, as well as effects on the adenylate cyclase system, including the downstream effector cyclic adenosine monophosphate response element-binding protein (Conti *et al.* 2007; Duman and Vaidya 1998; Nestler *et al.* 2002; Schloss and Henn 2004). Recent evidence indicates that ECS increases survival and neuronal differentiation of newborn dentate cells (Ueno *et al.* 2019).

Other studies indicate that neurogenesis in the dentate gyrus of adult rodents results in survival of functional neurons that contribute to synaptic transmission (Song *et al.* 2002), suggesting that antidepressants, including ECT, may ultimately improve hippocampal function. Hippocampal changes are accompanied by increases in local angiogenesis and blood flow in specific subregions of the hippocampus (Hellsten *et al.* 2005; Newton *et al.* 2006), and other evidence indicates that ECS increases autophagy and membrane trafficking in the hippocampus, effects that could contribute to neurogenesis and reductions in cellular stress (Enomoto *et al.* 2016; Otabe *et al.* 2014). Although studies in rodents indicate that neurogenesis contributes to some behavioral effects of medications (Santarelli *et al.* 2003) and stress resilience (Anacker *et al.* 2018), it is unclear whether similar neurotrophic effects occur with ECT in humans. Studies using magnetic resonance spectroscopy to monitor regional changes in the glutamate-to-glutamine ratio, a marker of local intracellular excitatory transmitter metabolism (Hasler *et al.* 2007), indicate that depressed subjects have low glutamate-to-glutamine ratios that normalize with effective ECT (Michael *et al.* 2003; Pfleiderer *et al.* 2003).

Indications for and Efficacy of Electroconvulsive Therapy

Major Depressive Disorder

The summary statement by the American Psychiatric Association Task Force on Electroconvulsive Therapy (2001) supported the efficacy and safety of ECT. A metaanalysis of randomized controlled trials (RCTs) performed by the UK ECT Review Group (2003) confirmed the following about the efficacy of ECT for major depressive episodes (MDEs):

- ECT is more efficacious than sham ECT (shown in six RCTs; effect size, 0.91).
- ECT is more efficacious than antidepressant pharmacotherapy (18 RCTs; effect size, 0.80).

Given these data, ECT should no longer be considered a treatment of last resort (Beale and Kellner 2000; Kellner *et al.* 2005). Instead, ECT should be viewed as a potential first-line treatment when a rapid clinical response is essential in severely ill patients (e.g., those with active suicidal ideation, catatonia, or a compromised medical condition related to depression such as dehydration or malnutrition), when the patient has a history of a positive response to ECT, or when the patient (or surrogate decision maker) requests ECT over other treatment options. ECT's antidepressant effects are more rapid than pharmacotherapy, and clinical trials have confirmed a rapid resolution of suicidal ideation with ECT (Kellner *et al.* 2005; Lin *et al.* 2020; Patel *et al.* 2006). ECT was associated with lower overall mortality rates (including suicide deaths) among depressed patients compared with no ECT in a large Danish national patient database. ECT also reduces psychiatric readmission rates (Jorgensen *et al.* 2020; Slade *et al.* 2017).

Beale and Kellner (2000) argued that reserving ECT for patients with multiple failed medication trials for MDEs does not factor in the tolerability and efficacy of modern ECT and may lead to needless suffering on the part of the patient. Based on data modeled from the landmark STAR*D study of a stepped pharmacotherapy/psychotherapy algorithm for depression treatment, ECT was demonstrated to be cost-effective when used after only two trials of pharmacotherapy or psychotherapy had failed (Ross *et al.* 2018).

Patients with MDEs could have underlying unipolar or bipolar depression. A recent metaanalysis demonstrated equivalent remission rates with ECT for both unipolar and bipolar depression, although bipolar depression has a slightly faster response rate (Bahji *et al.* 2019). A retrospective study also indicated similar decreases in suicide rates among patients with unipolar or bipolar depression treated with ECT (hazard ratio ~ 0.80) in comparison to matched controls (Liang *et al.* 2018).

Patients who have undergone ECT rated it as a highly effective treatment (Parker *et al.* 2001) and developed significantly more positive views of ECT after experiencing the treatment than they had before treatment (Schmitgen *et al.* 2020). About 85% of patients who have undergone ECT would agree to a second course of ECT if needed (Bernstien *et al.* 1998). Similarly, about 85% of patients in a later study rated ECT as beneficial and well tolerated (Brown *et al.* 2018). ECT-related relief of depressive symptoms has also been associated with long-term improvements in health-related quality of life (Giacobbe *et al.* 2018).

Predictors of Response

Consistent positive predictors of response and remission among patients with MDEs treated with ECT include older age and the presence of psychotic symptoms (Dombrovski *et al.* 2005; Haq *et al.* 2015; van Diermen *et al.* 2018). Other positive predictors of remission or response cited in several studies include greater psychomotor retardation, shorter duration of depressive episode, and greater depression severity (Haq *et al.* 2015; Heijnen *et al.* 2019; van Diermen *et al.* 2018). One analysis attributed the association between older age and ECT response to the higher rate of psychosis and psychomotor changes among depressed older adults rather than to age itself (van Diermen *et al.* 2020). Several recent studies have also reported that early symptomatic response (in weeks 1-2) to ECT is predictive of ultimate remission (Birkenhager *et al.* 2019; Lin *et al.* 2019; Martinez-Amoros *et al.* 2018). Patients with comorbid personality disorders and a history of medication treatment resistance may be less likely to respond to ECT (Feske *et al.* 2004; Haq *et al.* 2015; Heijnen *et al.* 2010; Nordenskjold *et al.* 2012; Rasmussen 2015; Yip *et al.* 2021).

A recent review of baseline neuroimaging predictors of ECT response in MDD indicated some evidence for the following positive predictors: lower hippocampal and anterior cingulate volume, higher amygdala volume, and connectivity between prefrontal and default mode networks. Negative predictors included deep white matter hyperintensities and medial temporal atrophy (Levy *et al.* 2019; Schmitgen *et al.* 2020). Several investigations have examined possible genetic determinants of ECT response in depression, with the most common candidates being genes regulating dopamine and serotonin function and growth factors such as brain-derived neurotrophic factor and vascular endothelial growth factor. Results have been largely inconsistent except for the catechol-O-methyltransferase gene. Homozygotes for the Val allele have increased catechol-O-methyltransferase activity, causing accelerated dopamine breakdown and a relative hypodopaminergic state that appears to increase the likelihood of responding to ECT (Benson-Martin *et al.* 2016). Efforts to correlate seizure characteristics with clinical outcome have been largely disappointing, the most consistent (albeit small) association being postictal depression predicting better response (Francis-Taylor *et al.* 2020).

Mania

Case studies and at least seven randomized clinical trials suggest that ECT is beneficial in the treatment of mania associated with bipolar disorder, demonstrating rapid effects and notable response rates (Elias *et al.* 2021; Fink 2001, 2006). Retrospective analysis of over 14,000 inpatients admitted from 2012 to 2014 for bipolar manic episodes in over 4,400 U.S. hospitals revealed that ~ 18% underwent ECT (Patel *et al.* 2019). In a prospective, controlled trial, Small *et al.* (1988) compared the efficacy of ECT with that of lithium in the treatment of mania. Patients who underwent ECT improved more during the first 8 weeks of treatment than did patients who received lithium. Nevertheless, after 8 weeks of treatment, ECT and lithium were comparable in efficacy. Other reports have suggested ECT may be more effective for acute mania than lithium and at least as effective as antipsychotics. ECT has proved helpful in cases of mania that were resistant to standard pharmacotherapies (Elias *et al.* 2021). The most notable limitation in prospective trials of ECT for mania is the small sample sizes; recruitment of this population is complicated by lack of patient insight into their diagnosis and higher standards for obtaining informed consent for ECT compared with pharmacotherapy.

A double-blind RCT of bifrontal and bitemporal ECT in acute mania also demonstrated the efficacy of ECT in mania (Hiremani *et al.* 2008). In addition, patients with mixed symptoms of depression and mania responded particularly well to ECT (Gruber *et al.* 2000; Medda *et al.* 2010, 2014; Valenti *et al.* 2008; Vieta 2005). Given the benefit of anticonvulsant medications in treating mania and the evidence that ECT may exert its therapeutic effect by raising the seizure threshold (Sackeim 1999), the efficacy of ECT for mania is not surprising. Catatonia secondary to mania and delirious mania represent other clinical scenarios in which ECT may offer advantages in efficacy and rapidity of response compared with pharmacotherapy (Elias *et al.* 2021; Taylor and Fink 2003).

Despite a rapid increase in studies evaluating alternative mood stabilizing medications, including newer anticonvulsants and atypical antipsychotics, there is a lack of research comparing the potential benefits of ECT in the acute and maintenance treatment of bipolar disorder (Fink 2001; Keck *et al.* 2000). This is regrettable given the advantages of ECT as a mood stabilizer that can effectively treat both the manic and the depressed phases of the illness. ECT has been given safely to children with intractable mania (Hill *et al.* 1997) and to patients with dementia and comorbid mania (McDonald and Thompson 2001). ECT also may have an important role in the treatment of mania during pregnancy, given the potential teratogenic effects of many anticonvulsant medications and the potential harm to both the mother and the fetus from a prolonged affective episode (Spodniakova *et al.* 2015).

It is unclear whether unilateral ECT is as effective as bilateral ECT in the treatment of mania. Hiremani *et al.* (2008) found both bifrontal and bitemporal ECT effective for mania with equivalent side-effect burden, although patients had a more rapid improvement with bifrontal electrode placement. Future research is needed to clarify the role of ECT in the treatment of mania, although clear evidence indicates that ECT is an effective treatment and should be included in any algorithm of therapy for treatment-resistant, severely disabling, catatonic, or delirious mania, as well as for mixed states (Jacobowski *et al.* 2013; Nivoli *et al.* 2012).

Schizophrenia

With the introduction of clozapine and the atypical antipsychotics, ECT has become a third-line treatment for schizophrenia in the United States, but ECT may be a first-line treatment for schizophrenia in some eastern hemisphere countries such as India and China (e.g., McDonald 2012). ECT continues to have an important role in the treatment of acute psychotic episodes, catatonic schizophrenia, and neuroleptic malignant syndrome (Matheson *et al.* 2010; Pompili *et al.* 2013; Tharyan and Adams 2005). The recommendations of the 2001) state that ECT is an effective treatment for schizophrenia during acute onset of symptoms, when the catatonic subtype of schizophrenia is present, and when there is a history of a positive response to ECT.

ECT is more beneficial for the treatment of positive symptoms of schizophrenia than for negative symptoms (Chanpattana and Sackeim 2010; Pawelczyk *et al.* 2014). Depressive disorders comorbid with schizophrenia may also respond favorably (Grover *et al.* 2020). ECT has also been shown to be effective in augmenting antipsychotic treatment in treatment-resistant schizophrenia (Painuly and Chakrabarti 2006; Ravanic *et al.* 2009). A Cochrane Database review (*n* = 1,285) concluded that moderate-quality evidence supported the efficacy of ECT added to standard care for medium-term clinical response among patients with treatment-resistant schizophrenia (Sinclair and Adams 2014). A randomized trial found bilateral ECT effective as an add-on to clozapine for treatment-refractory psychosis in schizophrenia, with a 50% response rate in this difficult-to-treat population (Petrides *et al.* 2015). A metaanalysis of 18 RCTs reported that the number needed to treat when adding ECT to clozapine was 4 for clinical response and 14 for remission, and the number needed to harm was 4 for subjective memory complaints (Wang *et al.* 2018). ECT may also improve symptom control when added to other antipsychotics for treatment-resistant schizophrenia, although, not surprisingly, ECT plus clozapine may be the most effective combination (Ahmed *et al.* 2017; Wang *et al.* 2015; Zheng *et al.* 2016). Maintenance ECT may help sustain this initial benefit among patients with schizophrenia on clozapine and others with schizophrenia who benefited from an initial course of ECT (Ward *et al.* 2018b; Youn *et al.* 2019).

ECT combined with neuroleptic therapy has been reported as effective in the management of aggressive behavior for patients with schizophrenia (Hirose *et al.* 2001), but analysis of seven RCTs from China showed no benefit for agitation over antipsychotic treatment in schizophrenia (Gu *et al.* 2017).

There has been research to support bifrontal (as opposed to bitemporal) electrode placement as providing better treatment response and tolerability in schizophrenia, although the data are limited (Bansod *et al.* 2018; Phutane *et al.* 2013).

As previously mentioned, catatonic schizophrenia is very responsive to ECT (Fink 2013; van Waarde *et al.* 2010). ECT can be an important treatment in cases where benzodiazepines are ineffective and patients do not respond to antipsychotics or antipsychotics are relatively contraindicated because of unclear diagnosis of catatonia versus neuroleptic malignant syndrome (Rosebush and Mazurek 2010).

Other Medical and Psychiatric Disorders

ECT can be a life-saving treatment for patients with catatonia regardless of the etiology, including catatonia resulting from a medical disease (e.g., systemic lupus erythematosus, neuroleptic malignant syndrome, *N*-methyl-D-aspartate receptor encephalitis) (Bica *et al.* 2015; Morcos *et al.* 2019; Warren *et al.* 2019). Response rates to ECT in catatonia of any origin are 80% or higher (Luchini *et al.* 2015). Patients with developmental delay complicated by catatonia, mood symptoms, or self-injurious behavior have experienced improvements in all these domains with ECT (Aziz *et al.* 2001; van Waarde *et al.* 2001; Wachtel *et al.* 2018).

A matched case-control study of over 22,000 patients with PTSD and MDD found that compared to antidepressant therapy alone, ECT combined with antidepressants was associated with a significant reduction of PTSD and MDD severity, as well as fewer completed suicides and lower cardiovascular and all-cause mortality (Ahmadi *et al.* 2016). However, RCTs for ECT treatment of PTSD are sparse and have low sample sizes.

Citing a case report of a decrease in PTSD symptoms when traumatic events were recalled immediately before each ECT session (Gahr *et al.* 2014), Andrade *et al.* (2016) hypothesized that ECT is effective because the treatment impairs reconsolidation of reactivated, emotionally aversive memories. A subsequent randomized trial failed to prove this hypothesis but did demonstrate effectiveness for PTSD comorbid with depression (Tang *et al.* 2021). Limited evidence (no RCTs) suggests that ECT may relieve symptoms associated with OCD (Fontenelle *et al.* 2015) and schizophrenia complicated by OCD (Lavin and Halligan 1996).

Case reports and retrospective reviews have demonstrated that ECT can alleviate behavioral and psychological symptoms of dementia, including associated depression, psychosis, and agitation. Such patients would be at increased risk of delirium during the acute course of ECT, but the limited existing evidence does not indicate significant worsening of the underlying dementia (Hermida *et al.* 2020, 2022; Liu *et al.* 2014; Rodriguez-Sosa *et al.* 2013; Tang *et al.* 2014; Ujkaj *et al.* 2012).

ECT may also be therapeutic for certain neurological diseases. The administration of ECT raises the seizure threshold, and ECT can interrupt status epilepticus (Pinchotti *et al.* 2018) and treat intractable seizures (Shah *et al.* 2012). ECT is effective in treating psychosis and depression in patients with Huntington's disease (Adrissi *et al.* 2019; Petit *et al.* 2016). ECT has also been demonstrated to improve motor symptoms of Parkinson's disease without worsening cognition (Faber and Trimble 1991; Kellner *et al.* 1994; Rasmussen and Abrams 1991; Takamiya *et al.* 2021). A metaanalysis of five studies reported that ECT acutely improves global motor functioning in patients with Parkinson's disease, with a notable effect size of 1.68 (Fregni *et al.* 2005). These reports have included patients with and without psychiatric illnesses; ECT improves the motor symptoms of Parkinson's disease independently of its effects on the patient's mood. Favorable predictors of response include advanced age, severe disability (on-off syndromes), and painful dyskinesias. Reduction in the symptoms of Parkinson's disease tends to occur during the first several sessions of ECT. However, the effects of ECT are not permanent and usually last from several days to several months, although prolonged improvement has been reported in a few patients. Maintenance ECT also has been shown to be effective for up to 4 years in treating the motor symptoms of Parkinson's disease (Aarsland *et al.* 1997; Wengel *et al.* 1998). As expected, ECT also improves depressive symptoms in persons with Parkinson's disease (Borisovskaya *et al.* 2016).

ECT has been reported to relieve pain symptoms associated with primary depression as well as pain among primary pain patients with secondary affective symptoms (Rasmussen and Rummans 2002), although acutely ECT may increase risk of headaches and musculoskeletal pain (Chahine *et al.* 2014). ECT may exert some analgesic effects independent of effects on mood, as evidenced in a trial with positive results using ECT to treat fibromyalgia (Usui *et al.* 2006). Similar positive results exist in case reports about ECT for refractory phantom limb pain (Rasmussen and Rummans 2000), neuropathic pain (Abdi *et al.* 2004), and complex regional pain syndromes (McDaniel 2003).

Electroconvulsive Therapy Use During Pregnancy

During pregnancy, ECT is an effective, safe treatment for women with severe manic and depressive symptoms according to a joint report by the American Psychiatric Association and the American College of Obstetricians and Gynecologists (Yonkers *et al.* 2009). As with pharmacotherapy, ethical concerns limit randomized prospective trials to assess efficacy and safety of ECT in pregnancy, although ECT has been safely used in all three trimesters of pregnancy (Rabheru 2001).

A review of 338 case reports from 1941 to 2007 identified 25 cases of fetal complications during ECT, of which less than half were deemed possibly or probably related to ECT, and 20 cases of maternal complications (90% of which were deemed possibly or probably related to ECT) (Anderson and Reti 2009). The efficacy rates among these case reports were in keeping with those of nonpregnant patients (61% for schizophrenia, 84% for depression). A more recent review likewise indicated a good safety profile for ECT during pregnancy. Risks for the mother were deemed comparable to those for nonpregnant patients, except for infrequent premature contractions and preterm labor. Reviewers reported a lack of evidence that ECT increases risk for miscarriages or congenital anomalies (Ward *et al.* 2018a). Not all reviews have reached the same conclusions, however. One review reported additional and more frequent adverse events with ECT during pregnancy, probably because there was no attempt at causal attribution (i.e., due to ECT vs. other causes) for adverse events, unlike in other reviews (Coshal *et al.* 2019).

The risks of administering ECT during pregnancy have been reviewed by Rabheru (2001). Possible strategies to mitigate these risks include obstetrics consultations and performance of the procedure in facilities equipped to deal with obstetric emergencies. Physiological problems in pregnancy that could affect ECT risks include delayed gastric emptying, aortocaval compression causing placental insufficiency, uterine restriction on respiratory ventilation when supine, and seizure-induced elevations in oxytocin and subsequent premature uterine contractions. Use of antacids, adequate hydration, elevation of the right hip, fetal heart rate monitoring, and availability of tocolytic therapy if needed are strategies to address these respective pregnancy-specific issues in ECT administration (Saatcioglu and Tomruk 2011; Ward *et al.* 2018a). The risks of ECT in pregnancy must be considered in context; there are also potential risks for the mother and fetus with untreated mental illness as well as with use of psychotropic medications, some of which have known teratogenic effects (Ward *et al.* 2018a).

FDA Final Order on Reclassifying Electroconvulsive Therapy Devices

On December 26, 2018, the FDA issued a final order or regulatory document on the reclassification of devices for the administration of ECT (U.S. Food and Drug Administration 2018). This document provides regulatory guidance on how device manufacturers can market their products in the United States. The FDA recategorized ECT devices from Class III to a less restrictive class, Class II, when marketed "for the treatment of catatonia or a severe MDE associated with MDD or bipolar disorder in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition." However, the FDA left several diagnostic categories in Class III that are commonly treated with ECT, including schizophrenia and mania. This was despite the efforts by the American Psychiatric Association and other groups to argue for a less restrictive classification for many of these psychiatric diagnoses (Binder and Levin 2016).

A Class II category permits manufacturers to sell devices for these diagnoses provided they include "special controls" in the labeling, which include pre-ECT medical and psychiatric assessment, patient monitoring during the procedure, use of general anesthesia and neuromuscular blocking agents, mouth and dental protection during the procedure, electroencephalogram (EEG) monitoring during an ECT-induced seizure to the point of seizure termination, adequate skin preparation and use of conductive gel for stimulus electrode placement, and cognitive status monitoring of the patient before and during ECT. They also include the importance of clinical training for practitioners and patient information in the form of brochures, leaflets, or videotapes to inform patients and their families about the relevant risks and side effects of ECT.

What are the clinical implications of the final order? The final order specifies that the "FDA is not permitted to limit or interfere with the authority of a health care professional to administer any legally marketed device to a patient for any condition or disease within a legitimate clinician-patient relationship" and that "FDA does not regulate off-label use of ECT by physicians." The off-label use of ECT is similar to the off-label use of medications. The physician should document both the risks and benefits of the procedure compared to other treatment options and should document the consent process. As was discussed in the previous section, ECT has been used for indications with research evidence for efficacy that were not necessarily part of the FDA indications for ECT, including neuroleptic malignant syndrome, self-injurious behavior in autism, agitated dementia, and PTSD. These indications would also be considered "off label."

For further information on the final order and relevance to clinical practice, see the resource document on the FDA final order to reclassify ECT devices prepared by an

American Psychiatric Association work group (Binder and Levin 2016) and other commentaries (Kellner *et al.* 2019; McDonald *et al.* 2016).

Administration of Electroconvulsive Therapy

Stimulus Dosing in Electroconvulsive Therapy for the Treatment of Depression

Questions about the proper management of the electrical stimulus have been central to the science and practice of ECT. Cerletti and Bini modeled ECT on the success of pharmacologically induced convulsive therapy and assumed that the stimulus should be convulsive. Interestingly, the first ECT session in 1938 involved two subconvulsive stimulations before Cerletti and Bini increased the stimulus intensity to produce a convulsion (Endler 1988). Therefore, this first session was a "titrated" ECT session with serial applications of increasing stimulus intensities passing from the subconvulsive range through the convulsive threshold. Issues in stimulus dosing that have been considered since that time include the following:

- Whether the stimulus should be subconvulsive or convulsive
- What the optimal stimulus waveform is
- If a convulsive stimulus is desired, to what degree the stimulus intensity should be in excess of the convulsive threshold
- Which physiological parameters, if any, provide useful feedback to continuously refine stimulus dosing throughout the ECT course

Convulsive, Subconvulsive, and Sham Stimulation

The use of nonconvulsive electrical stimulation to treat psychiatric disorders preceded the introduction of ECT by decades. Most of the treatments involved administering static electricity to parts of the body, including the head (Grover 1924). The availability of commercial ECT devices did not lead to the immediate replacement of subconvulsive stimulation with convulsive stimulation. Instead, some practitioners used the devices to deliver lengthy (several minutes long) subconvulsive cranial stimulation. However, it became clear that subconvulsive stimulation was associated with a poorer outcome than conventional psychotherapy in patients on the depressive/anxious spectrum, and the practice of treating patients with subconvulsive stimuli decreased (Hargrove *et al.* 1953). The elements of modified ECT (including muscle relaxation and general anesthesia) were described early in the history of ECT. The wide-scale adoption of these modifications raised new questions as to whether seizure is central to the antidepressant efficacy of ECT or whether anesthesia alone would be just as effective. The Northwick Park trial (Johnstone *et al.* 1980) and the Leicestershire trial (Brandon *et al.* 1984) are two examples of "sham" ECT studies in which anesthesia alone was compared with real ECT. It was convincingly demonstrated that real ECT is more efficacious, especially for the most severe forms of depression (Brandon *et al.* 1984; Johnstone *et al.* 1980). The efficacy of ECT was clearly linked to the production of a seizure. Neither the use of anesthesia alone without the electrical

stimulus nor the use of subconvulsive electrical stimuli appears to have real benefit in the treatment of depression.

Stimulus Waveform

Given that a convulsive stimulus is necessary for the antidepressant effects of ECT, a nearly infinite number of variations are available for formulating the stimulus waveform. The earliest ECT devices delivered a sinusoidal stimulus. Other waveforms available on early ECT devices included the "chopped" sine wave, the unidirectional pulse square wave, and the alternating brief-pulse square wave. Although some investigators suspected that sine wave stimuli might produce slightly better antidepressant effects than did brief-pulse stimuli, that suspicion was mitigated by a randomized study showing that sine wave ECT produced more memory side effects than brief-pulse ECT, irrespective of the placement of the stimulating electrode (Weiner *et al.* 1986b).

This finding of greater cognitive side effects with sine wave ECT was replicated in an efficacy study with a prospective cohort design, which showed that compared with brief-pulse stimulation, sine wave stimulation was associated with a slowing of reaction time that persisted for at least 6 months after ECT (Sackeim *et al.* 2007). The more severe cognitive side effects produced by sinusoidal stimuli may be explained by the slower rise time for each sine wave cycle as compared with the brief-pulse cycle. Consequent to the slower rise time, much of the sine wave stimulus is subconvulsive and thus presumably adds nothing to the therapeutic effect of ECT, adding only to cognitive side effects. The steep rise in the brief-pulse waveform allows the entire stimulus to be above the convulsive threshold (suprathreshold). Because much of the sine wave stimulus is nonproductive, being in the subconvulsive range, it was predicted that brief-pulse stimuli would be more efficient, requiring a stimulus of smaller magnitude to produce a seizure. Standard brief-pulse stimuli are defined by a pulse duration of 1-2 milliseconds, and ultrabrief-pulse stimuli are defined by a pulse duration of < 0.50 milliseconds. In 1980, Weiner showed that standard brief-pulse stimuli could provoke a seizure with only one-third of the energy required with sine wave stimuli (Weiner 1980). Standard brief-pulse ECT devices have currently replaced sine wave devices in the United States (Farah and McCall 1993).

Devices using ultrabrief-pulse stimuli have the advantage of increasing the efficiency of seizure induction. Abrams (2002) estimated that it takes only about 0.25 milliseconds to initiate neuronal depolarization, and wider pulse widths are inefficient and waste electrical charge. The total energy output of these ultrabrief-pulse modalities is the same as the total energy output of the standard brief-pulse widths; thus, as the stimulus pulse widths are shortened, the stimulus trains are lengthened. Ultrabrief pulse widths may have an advantage because shorter pulse widths and longer pulse trains have been shown to elicit seizures with a smaller electrical charge and therefore may have fewer cognitive side effects (Sackeim *et al.* 2008). Even in older patients with MDD, ultrabrief pulses induce seizures 84% of the time with stimuli of only 5% of the maximal ECT device output in the United States (Kellner *et al.* 2016b). This is remarkable and relevant because older patients have high seizure thresholds.

Several recent studies have assessed the efficacy and side-effect profile of brief-versus ultrabrief-pulse-width right-unilateral (RUL) ECT in MDD. In a prospective study comparing ultrabrief-pulse RUL ECT (0.3 millisecond; *n* = 74) versus brief-pulse RUL ECT (1.0 millisecond; *n* = 22) in depressed individuals, Loo *et al.* (2008) found similar depression response rates in the two groups (but a slower rate of response in the ultrabrief-pulse RUL ECT group), with better cognitive outcomes in the ultrabrief group. In a prospective randomized trial of high-dose RUL ECT in 87 depressed inpatients, Spaans *et al.* (2013a) found that patients undergoing ultrabrief-pulse ECT were significantly less likely to achieve remission--and needed significantly more treatments to do so--compared with patients receiving brief-pulse ECT. A retrospective study of 150 subjects pooled from three research samples found that fewer treatments were needed with brief-pulse than with ultrabrief-pulse RUL ECT and that remission rates were significantly higher with brief-pulse ECT (Loo *et al.* 2003). Generally, researchers have found that ultrabrief-pulse RUL ECT produced fewer neurocognitive effects (specifically on autobiographical memory) compared with brief-pulse treatment (Mayur *et al.* 2013; Verwijk *et al.* 2012) or that side effects for the two types were similar (Spaans *et al.* 2013b). Recently, Kellner *et al.* (2016b) showed that ultrabrief-pulse RUL ECT produces remission from MDD in 61.7% of depressed older adults. The same group also showed that continuation therapy with ultrabrief-pulse RUL ECT and psychotropics is more effective than psychotropics alone in maintaining remission in MDD (Kellner *et al.* 2016b). Very preliminary evidence suggests that ultrabrief-pulse RUL ECT may be effective in treatment-resistant mania (Elias *et al.* 2019; Wong *et al.* 2019).

The data on pulse width and bilateral ECT are also evolving. In a retrospective study of bilateral ECT in which 65 patients with MDD received a pulse width of either 0.5 millisecond (brief) or 0.25 millisecond (ultrabrief), the two groups had similar response and remission rates (Niemantsverdriet *et al.* 2011). In a prospective randomized trial in which 64 patients received treatment with a course of either bifrontal ultrabrief-pulse (0.3 millisecond) ECT at 1.5 times the seizure threshold or RUL ultrabrief-pulse ECT at 6 times the seizure threshold, the two patient groups showed equivalent response rates, with no changes in cognition in either group (Sienaert *et al.* 2010).

However, a randomized trial of 90 depressed patients who were treated with either RUL ECT at 6 times the seizure threshold or bilateral ECT at 2.5 times the seizure threshold, using either a traditional brief pulse (1.5 milliseconds) or an ultrabrief pulse (0.3 millisecond), found that the remission rate with ultrabrief-pulse bilateral ECT was significantly lower than that with brief-pulse bilateral ECT (35% vs. 65%). Ultrabrief-and brief-pulse RUL ECT (remission rates of 73% and 59%, respectively) were as effective as brief-pulse bilateral ECT (65%) but produced fewer cognitive side effects. Of the four treatment groups, ultrabrief-pulse RUL ECT was associated with the fewest cognitive side effects (Sackeim *et al.* 2008).

A systematic review concluded that brief-pulse-width RUL ECT was "slightly" more efficacious in treating depression and required fewer treatment sessions but was also associated with more cognitive side effects (Tor *et al.* 2015). Other groups have reviewed the data and argued against the use of ultrabrief RUL ECT, saying the evidence does not support its use as a first-line treatment when compared to brief-pulse RUL (Spaans *et al.* 2013b) or brief-pulse bilateral ECT at 2.5 times the initial seizure threshold (McCormick *et al.* 2009) as the first-line treatment. Clinicians considering the use of brief-pulse RUL versus ultrabrief-pulse RUL ECT versus bilateral ECT should take into account clinical factors such as baseline cognitive or neurological status and the severity of psychiatric symptoms, as well as practical issues such as the potential for increased length of the treatment course with ultrabrief-pulse treatments (Galletly *et al.* 2012, 2014).

The picture with ultrabrief bilateral ECT is less clear, and further research may be needed to determine the efficacy of ultrabrief compared to standard brief-pulse bilateral ECT. Some have argued that brief-pulse RUL should be used when a faster response is needed and brief-pulse bilateral

ECT should be used until the research data support the efficacy of ultrabrief bilateral ECT (Loo *et al.* 2012b).

Magnitude of the Stimulus Dose

The consensus regarding the need for convulsive (as opposed to subconvulsive) stimuli and brief-pulse waveforms would seem to make stimulus dosing in ECT a straightforward process, except for the question of the degree to which the stimulus should exceed the convulsive threshold. For years, ECT practitioners were satisfied that the answer to this question was found in the work of Ottosson (1962), who compared routine ECT with ECT modified by pretreatment with intravenous lidocaine. He found that seizures induced by lidocaine-modified ECT were shorter than those induced by routine ECT and observed an inverse relationship between seizure duration and antidepressant effect. From this work, it was widely accepted that stimulus doses producing seizures lasting at least 25 seconds have an antidepressant effect (American Psychiatric Association Task Force on Electroconvulsive Therapy 1978).

Initially, ECT was administered with bilateral (typically bitemporal) electrode placement. In 1949, Goldman introduced RUL ECT and placed stimulating electrodes over the right hemisphere rather than the mesial temporal lobes to decrease the direct stimulation of language areas and decrease cognitive side effects (Goldman 1949). Although RUL ECT was associated with fewer cognitive side effects, most studies showed that bilateral ECT had a marked therapeutic advantage over unilateral ECT for depression (d'Elia and Raotma 1975).

The clinical wisdom that bilateral ECT was more effective than RUL ECT in treating depression came into question with the work of Sackeim's research group. Sackeim *et al.* (1993) reported that when the magnitude of the electrical stimulus was just barely above the convulsive threshold, ECT with RUL electrode placement was not efficacious, despite the production of electrographic seizures typically in excess of 25 seconds. However, as the electrical dose was progressively increased, response rates in RUL ECT improved significantly and approached those of bilateral ECT. In contrast, bilateral ECT was fully efficacious with stimuli minimally above or 2.5

times the seizure threshold, but excess memory side effects accrued at the higher stimulus dose.

There is a dose-response relationship in RUL ECT only to the extent that the stimulus dose exceeds the convulsive threshold for a given patient; the absolute magnitude of the stimulus dose has no independent influence on this relationship. The efficacy of RUL ECT follows a nearly linear relationship to the degree that the stimulus dose exceeds the seizure threshold, at least through 12 times the seizure threshold (McCall *et al.* 2000). This relationship is analogous to the pharmacological treatment of depression with tricyclic antidepressants: serum blood levels are more important than the absolute oral dose in determining both efficacy and side effects.

These findings led to the following conclusions:

- With standard brief-pulse stimulation delivered with RUL electrode placement, the stimulus should be substantially above the convulsive threshold in order to ensure the effectiveness of ECT.
- With standard brief-pulse stimulation delivered with bilateral electrode placement, the stimulus should not be excessively above the convulsive threshold, in order to avoid undue cognitive side effects.

The convulsive threshold varies by a factor of at least 40 in large patient samples; thus, the mean threshold for a group of patients may not inform the threshold for an individual (Sackeim *et al.* 1991). It is clear that the convulsive threshold is related to age, sex, race, choice of stimulating electrode placement, and, perhaps, cranial dimensions (Chung 2006; Colenda and McCall 1996; Sackeim *et al.* 1991) and even volume of cerebrospinal fluid estimated on MRI (van Waarde *et al.* 2013). Still, these factors predict only a small amount of the variance in the convulsive threshold, and statistical models to predict the convulsive threshold, including age-based dosing approaches, may not yield an accurate estimate of the threshold (Colenda and McCall 1996; Tiller and Ingram 2006). In addition, a primary factor for an individual patient may be medications that affect the seizure threshold (e.g., benzodiazepines, anticonvulsants), which are difficult to account for in any algorithm estimating the seizure threshold.

Seizure Morphology

The report of Sackeim *et al.* (1993) that threshold RUL ECT produced seizures of 25 seconds or longer without antidepressant efficacy cast doubt on the clinical wisdom that the stimulus dose was therapeutic if the electrographic seizure lasted at least 25 seconds. Investigators have sought a physiological marker of treatment adequacy to replace seizure duration. The most promising candidate is seizure morphology. Ottosson (1962) reported that lidocaine changed the shape of ECT seizures and affected their duration, although the first finding is largely overlooked. Lidocaine-modified seizures, in addition to being less efficacious than standard ECT seizures, were characterized by loss of spike activity and poor postictal suppression.

Seizure morphology varies according to ECT technique. That is, greater seizure intensity correlates with ECT techniques that progress from lower efficacy (with RUL electrode placement and low stimulus intensity) to higher efficacy (with bilateral placement and high stimulus intensity) (Krystal *et al.* 1993). Electrode placement and stimulus intensity have independent and additive effects on seizure morphology. Seizures of greater intensity are characterized by higher peak ictal amplitudes, greater stereotypy of the ictal discharge, greater symmetry and coherence between the left and the right cerebral hemispheres, and more profound postictal suppression. The natural extension of this reasoning leads to the hope that seizure morphology could guide decisions about stimulus intensity as the course of ECT progresses. For example, if seizure intensity is low in the middle of the treatment course, then the treatment technique should be changed (by switching electrode placement or increasing the stimulus intensity) in order to optimize the clinical outcome. Manufacturers of ECT devices now incorporate automated measures of seizure intensity into the ECT chart recorder, and the accompanying owner's manual instructs the practitioner to increase the stimulus intensity if the seizure morphology appears to be degraded. The unstated implication is that degraded seizure morphology is a problem and that increasing the stimulus intensity will fix the problem. This instruction might have merit if stimulus intensity were the primary determinant of seizure morphology, but other factors, such as age, baseline convulsive threshold, and other intrinsic patient characteristics, probably play an equal role in determining seizure expression (McCall *et al.* 1996, 1998). For example, greater seizure durations coupled with greater seizure regularity, as shown by electroencephalography at the second ECT session, are predictive of a better antidepressant outcome at the conclusion of the ECT course, and this relation is independent of the choice of stimulus electrode placement (Kimball *et al.* 2009).

Seizure morphology is little influenced by increasing the stimulus intensity above 2.5 times the seizure threshold. Therefore, it is premature to recommend stimulus dosing based on seizure morphology. The importance of seizure morphology in predicting clinical outcome is not well understood, and more work is needed if seizure morphology is to become a practical tool for governing ECT technique. Peak heart rate has been proposed as an alternative physiological measure of treatment adequacy, with higher heart rates perhaps indicating better clinical outcomes (Swartz 2000). Again, this approach has yet to be widely accepted.

Integrating the Science of Stimulus Dosing With the Choice of Electrode Placement

Estimating the convulsive threshold. The recent advances in knowledge pertaining to stimulus dosing led to the conclusion that standard brief-pulse RUL ECT should be initiated with a stimulus known to be at least five times the seizure threshold, whereas standard brief-pulse bilateral ECT should be initiated with a stimulus about 50% above the seizure threshold. Choosing between these two strategies requires consideration of both efficacy and side effects. However, ultrabrief RUL ECT should be considered when patients are at risk for cognitive complications from ECT (e.g., Parkinson's disease).

McCall *et al.* (2000) conducted a randomized comparison of low-dose (1.5 times the seizure threshold) bilateral ECT (*n* = 37) and high-dose (8 times the seizure threshold) RUL ECT (*n* = 40). Again, depression remission rates were not significantly different with RUL electrode placement (60%) versus bilateral placement (73%), and memory effects were likewise similar. This study can be criticized for having insufficient power to detect small but meaningful effects. However, that concern was addressed in a subsequent study (Sackeim *et al.* 2009) involving 319 patients randomly assigned to receive either standard brief-pulse RUL ECT administered at 6 times the seizure threshold or bilateral ECT administered at 1.5 times the seizure threshold. Although differences between the electrode placements' antidepressant effects were again indistinguishable, the extent of autobiographical memory loss was greater in the bilateral group.

Kellner *et al.* (2010) conducted a multicenter double-blind, controlled trial in which 230 patients with MDD were randomly assigned to one of three electrode placements: bifrontal at 1.5 times seizure threshold, bitemporal at 1.5 times the seizure threshold, and RUL at 6 times the seizure threshold. They found that all three electrode placements were statistically equivalent, with remission rates of 55% with RUL, 61% with bifrontal, and 64% with bitemporal electrode placements. Notably, the patients treated with bitemporal electrode placement had more improvement in depression early in the course of treatment. In this study, the investigators used a very complete neuropsychological battery including measures of autobiographical memory and found few differences between the electrode placements on a variety of neuropsychological instruments.

The bulk of the evidence thus suggests that it is desirable to set the stimulus dose as a proportion of the convulsive threshold. The convulsive threshold of each patient should be identified, preferably by measuring convulsive threshold early in the ECT course. The most accurate means of measuring the convulsive threshold for a given patient is empirical observation through use of stimulus "titration" at the initial treatment session, a technique in which an intentionally subconvulsive stimuli is first administered, followed by administration of successively larger stimuli until a seizure is produced. This approach applies to both RUL and bilateral electrode placement.

If ECT practitioners agree with the above reasoning and use this stimulus dosing technique, they should ascertain the convulsive threshold at the first ECT session. However, some ECT researchers have argued against titration of stimulus doses with unilateral ECT and instead have encouraged practitioners to use fixed high doses of unilateral ECT (Abrams 2002) or fixed moderate doses of bilateral ECT (Kellner 2001). Concerns about stimulus dose titration include the risk that the subconvulsive stimulation inherent in stimulus titration might be medically dangerous, the subconvulsive stimulation might add to the memory side effects, or the production of a barely suprathreshold seizure with RUL placement could constitute ineffective treatment, thus rendering the first treatment a wasted effort.

Subconvulsive stimulation transiently slows the heart rate, and if a subconvulsive stimulation is administered to patients who have received a b-blocker and no anticholinergic drug, substantial asystole is a risk (McCall *et al.* 1994). However, atropine pretreatment eliminates this risk. The possibility of excess acute cognitive side effects with subconvulsive stimuli has been examined and discounted (Prudic *et al.* 1994). However, the possibility of a sluggish antidepressant response when RUL stimulus doses are titrated to a level moderately above the seizure threshold is a reasonable concern that must be weighed against the benefits associated with assessing the seizure threshold to determine the most therapeutic dose for ECT. Of course, an initial titrated suprathreshold bilateral stimulus would be closer to the therapeutic dose (or 1.5-2.5 times the seizure threshold), and the cognitive benefits of ensuring that the dose is not suprathreshold (i.e., > 3 times the seizure threshold) are more straightforward.

Alternatives to estimating the convulsive threshold. Abrams (2002) suggested that the most efficient method of administering RUL ECT is to use 100% of the maximum device capacity and a pulse width of 0.25-0.50 milliseconds and recommended changing to bilateral ECT if the patient does not improve sufficiently. This strategy takes advantage of the cognitive sparing of lower pulse widths and the efficacy of RUL ECT at high doses. The disadvantages of this strategy are the fact that it is not adjusted to the patient's seizure threshold and the potential for more cognitive side effects without therapeutic benefit.

Alternatively, twice-weekly bilateral ECT could be initiated using the half-age method (Abrams 2002). In the half-age method, the age of the patient is divided by 2; the resulting number is the percentage of the device's maximal output with which the patient is first treated (e.g., a 50-year-old would be treated at 25% of the machine's maximal output). The half-age method has been shown to be a reasonable estimate of therapeutic stimulation for patients undergoing bitemporal ECT (Petrides *et al.* 2009). As stated above, characteristics other than age that can influence a patient's seizure threshold include multiple medications (e.g., benzodiazepines, valproic acid) that the patient may be taking and anesthetic medications such as propofol. For these reasons, this calculation may be problematic.

Choosing an Electrode Placement and Stimulus Dose

Patients with the most serious complications of MDD or mania (i.e., active suicidal behavior with intent, catatonia, psychosis) should be considered for brief-pulse bitemporal ECT at 1.5-2.5 times the stimulus threshold. Consideration of high-dose (5-6 times the seizure threshold) brief-pulse (or ultrabrief-pulse) RUL ECT is appropriate given concerns about a patient's vulnerability to the cognitive side effects of ECT. No clear guidelines are available for use of RUL ECT in schizophrenia or mania, although some evidence supports bifrontal over bitemporal ECT in schizophrenia (Phutane *et al.* 2013) and acute mania (Hiremani *et al.* 2008).

Other situations favoring the use of titrated ultrabrief-pulse or brief-pulse RUL ECT (with its potential cognition-sparing effects) include treatment of depressed patients with comorbid dementia or other neurological conditions (e.g., Parkinson's disease). The treatment for these patients should minimize even transient memory side effects and may include starting at a very conservative unilateral dose (i.e., five times the seizure threshold) and increasing the dose as tolerated.

The length of a course of ECT is highly variable and may depend on the diagnostic problem that requires treatment. Courses of ECT for depression typically run for 6-10 sessions, and courses of ECT for schizophrenia may be much longer. The course length should be individualized, based on clinical response. Depressed patients rarely show major improvement after one or two sessions, only to rapidly relapse if the treatment course is terminated. At the other extreme, there is the risk of premature discontinuation of the treatment course if the patient has not achieved remission within an "average" number of sessions. If the ECT provider is considering a longer course of ECT because of failure to remit, there is a temptation to assume that the treatment technique during the additional, extended sessions should be changed to improve the chances for success (e.g., switching a depressed patient who has not remitted after eight RUL sessions to bilateral ECT). This practice has been challenged by recent evidence showing that switching to bilateral electrode placement for an extended course of ECT is highly likely to lead to remission regardless of whether the electrode placement in the first part of treatment was RUL or bilateral (Sackeim *et al.* 2020). This finding raises the possibility that it is not the switch in electrode placement that effected the remission but rather the additional treatments. This matter is not trivial as a midcourse switch to bilateral placement is associated with more severe autobiographical memory problems. The field would be helped by a clinical trial that compared switching to bilateral versus staying with RUL in depressed patients who require an extended course of ECT.

Electroconvulsive Therapy Treatment Procedure

Pretreatment Medical Evaluation

Although no medical condition is an absolute contraindication for ECT, several clinical conditions may increase the risk of complications from ECT (Tess and Smetana 2009):

- Recent myocardial infarction or unstable cardiac conditions

- Implanted cardiac devices
- Atrial fibrillation
- Any illness that increases intracranial pressure (e.g., brain tumor)
- Recent cerebral infarction, particularly hemorrhagic infarction
- Obstructive pulmonary disease or asthma
- Aneurysm or vascular malformation
- American Society of Anesthesiology physical status classification level 4 or 5

When treating high-risk patients with ECT, clinicians must evaluate the effects of ECT on cerebral and cardiac physiology and review data from the extant ECT literature to help develop individual risk-benefit ratios (American Psychiatric Association Task Force on Electroconvulsive Therapy 2001; Saito 2005; Sundsted *et al.* 2014). All patients should undergo a thorough medical and neuropsychiatric review before beginning ECT. Emphasis should be placed on diseases affecting the CNS and the cardiovascular system. The pre-ECT evaluation should include a physical examination, detailed neurological examination, mental status examination, medical history, and review of systems. The patient's mental status should be evaluated before initiation of ECT and monitored closely before administration of ECT at every session thereafter.

ECT Administration

ECT sessions usually are scheduled for the morning. The patient's bladder should be emptied before treatment. Patients should not eat or drink for at least 8 hours before receiving the treatment. Famotidine or ranitidine is given the night before and the morning of ECT to neutralize the patient's gastric contents. Alternatively, sodium citrate can be given the morning of the treatment and will have an effect within 5-10 minutes.

The patient should be instructed to limit the number of medications, and the water needed to swallow the medications, on the morning of ECT to cardiac medications (except lidocaine, which is an anticonvulsant), pulmonary medications (except theophylline, which has been associated with status epilepticus after an ECT treatment), and glaucoma medications (except cholinesterase inhibitors, e.g., echothiophate). Given that the patient's oral intake is restricted, clinicians should also consider withholding any diuretics until after the treatment, depending on the patient's cardiac status. In diabetic patients, hypoglycemic medications are usually withheld on the morning of treatment to minimize the risk of hypoglycemia in a patient who is taking nothing by mouth. The patient's blood sugar level should be checked before ECT, and hyperglycemia or hypoglycemia should be treated appropriately. An ECT treatment will result in a modest short-term increase in the patient's blood sugar. In general, patients with epilepsy or mania should continue taking their anticonvulsants during ECT. If difficulty arises in eliciting seizures, decreasing the dose of the anticonvulsant can be considered.

The standard anesthetic agent in the United States is methohexital, a short-acting barbiturate with limited anticonvulsant effects. Methohexital is given in a dose of approximately 0.75-1.0 mg/kg. An alternative anesthetic is propofol (0.75-1.50 mg/kg), which is associated with shorter seizures than methohexital and an increase in the number of missed seizures (i.e., delivery of an electrical stimulus without induction of a seizure) (Swaim *et al.* 2006). However, seizure duration has not been correlated with clinical efficacy (Sackeim *et al.* 1991), and trials comparing the use of methohexital versus propofol have not shown significant differences in the antidepressant efficacy of ECT (Avramov *et al.* 1995; Rasmussen 2014). Propofol is associated with improved hemodynamic stability and equivalent improvement in depressive symptoms in studies comparing the two anesthetic agents (Geretsegger *et al.* 2007) and has advantages in improved hemodynamics and a quicker postanesthesia recovery time (Rasmussen 2014).

Immediately after the patient is anesthetized, a muscle relaxant is administered intravenously. Succinylcholine, at doses of 0.75-1.50 mg/kg, is a widely used depolarizing blocking agent. In patients with a pseudocholinesterase deficiency, catatonia (which can lead to cardiac complications due to immobility and hyperkalemia with succinylcholine [Zisselman and Jaffe 2010]) or a musculoskeletal disease, a nondepolarizing agent such as rocuronium can be considered. The combination of rocuronium and sugammadex has been shown to reduce myalgia and headache after ECT (Saricicek *et al.* 2014).

Anticholinergic agents, such as atropine or glycopyrrolate, are used to prevent ECT-induced bradycardia and to minimize airway secretions. Glycopyrrolate does not cross the blood-brain barrier and therefore may be associated with less postictal confusion than atropine in older individuals. When a b-blocker is added to control the ECT-induced rise in blood pressure and heart rate, an anticholinergic agent should be considered since the initial response to the ECT stimulus is bradycardia. Atropine (0.4-1.0 mg) or glycopyrrolate (0.2-0.4 mg) can be given either intramuscularly 30 minutes before the ECT treatment or intravenously at the time of treatment.

Regarding dosing of the electrical stimulus, the titration or method-of-limits approach uses a table with incremental increases in the electrical energy to determine the minimal amount of energy necessary to produce a seizure (the seizure threshold) as monitored by electroencephalography. Typically, a seizure lasting 30-90 seconds occurs during treatment.

Seizures lasting longer than 3 minutes should be terminated by administering an anticonvulsant (e.g., a second dose of methohexital or propofol, or a short-acting benzodiazepine such as midazolam). Patients usually are alert and oriented 20-45 minutes after receiving an ECT treatment.

Strategies for Addressing Shortened, Missed, or Abortive Seizures

Seizure quality and duration can decrease during the course of ECT because ECT-induced seizures have anticonvulsant properties. As discussed above, seizure length is not related to clinical outcome. But there are several strategies to consider if a patient is not improving clinically and has short or poorly formed seizures. These strategies include hyperventilation, changing anesthetic agents or lowering the anesthetic agent and supplementing with short-acting opiates, increasing the spacing between electrodes to decrease shunting, increasing the patient's hydration, adding flumazenil for patients on benzodiazepines, and increasing the stimulus dose (Weiner and Reti 2017). Anticonvulsant medications (i.e., benzodiazepines, carbamazepine, valproic acid, lamotrigine) can also be held the night before an ECT treatment. Flumazenil (0.4-1.0 mg), a benzodiazepine antagonist, has been used to block the anticonvulsant

effects of benzodiazepines, although it has not been shown to increase the efficacy or seizure duration of an ECT treatment (Krystal *et al.* 1998).

Changing to the anesthetic etomidate (0.15-0.3 mg/kg) from methohexital or propofol is associated with significantly longer seizures (Stadtland *et al.* 2002), which does not appear to be dose dependent (van Lammeren *et al.* 2013). In one retrospective naturalistic study, etomidate was associated with a significantly shorter treatment course (Swaim *et al.* 2006).

Another approach to address shortened or abortive seizures is to supplement methohexital or propofol with an ultra-short-acting narcotic such as remifentanil or alfentanil and to decrease the dose of the methohexital or propofol. These opiates are potentially proconvulsant and suppress the hemodynamic response to the seizure and can provide anesthesia that will allow lower doses of methohexital or propofol (Locala *et al.* 2005; Vishne *et al.* 2005).

Ketamine (1-2 mg/kg), which has a minimal effect on the seizure threshold (Hoyer *et al.* 2014; Wang *et al.* 2012), can also be used as the anesthetic agent or as an adjunctive anesthetic agent, with the caveat that ketamine can prolong recovery and may exacerbate psychosis. However, data on the use of ketamine in ECT are still preliminary (Galvez *et al.* 2017). There is limited evidence that the use of ketamine as an anesthetic agent can augment the antidepressant response of ECT (Anderson *et al.* 2017; Loo *et al.* 2012a).

Caffeine sodium benzoate (usual dose, 120-140 mg) may be administered intravenously during ECT to maintain adequate seizure duration (Coffey *et al.* 1990). Caffeine lengthens the seizure duration during ECT without lowering the seizure threshold (McCall *et al.* 1993). At present, it is not known whether caffeine augments the antidepressant effects of ECT or increases the speed of response to ECT. Theoretically, caffeine would have little therapeutic effect on unilateral ECT, because the length of the seizure is less important than the degree to which the seizure stimulus exceeds the seizure threshold.

Management of Electroconvulsive Therapy-Related Side Effects

Headaches, Muscle Soreness, and Nausea

Headaches are a common side effect of ECT, occurring in about 5%-7% of patients (Sato *et al.* 2013), and in most cases are mild. However, they can be throbbing, usually over the forehead, and be accompanied by nausea and vomiting. Patients who experience frequent post-ECT headaches may benefit from prophylactic treatment such as aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs (e.g., intravenous ketorolac) given before the ECT treatment. For patients with a history of migraines, pretreatment with subcutaneous or intranasal sumatriptan or another migraine medication should be considered.

Muscle soreness is common after the first treatment because of intense fasciculations following administration of a depolarizing muscle relaxant (succinylcholine). It can be treated symptomatically with analgesic agents such as aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs. Generally, muscle soreness decreases with subsequent treatments and is more common in younger patients. Severe symptoms can be managed by switching the paralytic agent to the nondepolarizing agent rocuronium, which has also been demonstrated to decrease post-ECT headaches (Saricicek *et al.* 2014).

Nausea is also a relatively common side effect of ECT. It may accompany a headache or occur independently. Nausea can be treated with prochlorperazine, ondansetron, or metoclopramide, which can be given prophylactically for susceptible patients.

Cardiovascular Side Effects

ECT is associated with an increased risk of cardiovascular complications in older adults who have, or who are at risk for, cardiovascular disease. Studies have found widely varying rates of cardiac complications in older adults undergoing ECT. The retrospective design of the studies, the lack of continuous cardiovascular monitoring, and the different definitions of what constitutes a cardiac complication probably account for the discrepancies in the results. Despite the inconsistencies, most studies have found a correlation between cardiac complications and age. ECT often produces transient systemic hypertension and abrupt transitions in cardiac rate, which can result in myocardial ischemia or arrhythmias. The higher incidence of cardiac complications among older adults is probably associated with the higher rate of preexisting cardiac conditions such as hypertension, coronary artery disease, and arrhythmias. On the basis of these observations, several authors have recommended the use of prophylactic cardiac medications to dampen cardiovascular responses during ECT in older adults who have (or are at risk for) cardiovascular disease.

Research has documented that labetalol (a medication with both a- and b-adrenergic blocking activity), esmolol (a shorter-acting b-blocker) (Castelli *et al.* 1995; Shrestha *et al.* 2007), and nicardipine (a calcium channel blocker) (Avramov *et al.* 1998; Zhang *et al.* 2005) can be safely used to attenuate the cardiac response during ECT.

It is recommended that adequate doses of an anticholinergic medication (intravenous atropine or glycopyrrolate) be used to decrease bradycardia induced by the initial stimulus (Swartz and Saheba 1989), and anticholinergic medications given before ECT have also been shown to increase cerebral oxygenation and perfusion during the seizure (Rasmussen *et al.* 2007). To help prevent ECT-induced hypotension, it is additionally recommended that all patients be adequately hydrated before undergoing ECT. If patients experience significant orthostatic hypotension in the recovery room, labetalol can be switched to the shorter-acting pure b-blocker esmolol.

The anesthetic agent propofol has been shown to have less cardiovascular effects than methohexital and can be used for patients with preexisting cardiac conditions requiring an attenuated hemodynamic response during treatment (Bailine *et al.* 2003). As noted earlier, the trade-off is a shortening of the seizure length with the use of propofol.

Cognitive Side Effects

The greatest area of concern with ECT among the lay public, patients, and their families is the potential development of adverse cognitive changes (Rajagopal *et al.* 2013).

The medical community's concerns about cognitive side effects and the negative images of ECT in the media are important factors determining the availability of ECT.

The technique by which ECT is administered influences the incidence and severity of cognitive side effects that may develop during a course of ECT. Specifically, electrode placement, the type of electrical waveform, the intensity of the electrical stimulus, and the frequency of ECT sessions all affect cognitive outcomes during ECT. Preexisting structural brain changes (e.g., white matter hyperintensities), medical illness, advancing age, low cognitive reserve (assessed in relation to education and occupation), and concomitant administration of certain psychotropic medications also may be risk factors for cognitive side effects from ECT (McClintock *et al.* 2014; Oudega *et al.* 2014).

It is important to recognize that depression itself (especially late-life depression) often causes cognitive deficits, such that successful treatment of depression with ECT often improves some aspects of cognition in certain patients (Weiner and Reti 2017). In depressed patients, Hihn *et al.* (2006) demonstrated that prefrontally mediated aspects of cognition, such as attention and immediate encoding, improved during ECT treatment of depression, whereas long-term memory functions remained impaired. In a review and metaanalysis, Semkovska and McLoughlin (2010) analyzed 84 studies that reported on post-ECT cognitive measures among a combined cohort of 2,981 patients; their findings included evidence that beyond 14 days after termination of the ECT course, several cognitive domains (processing speed, verbal working memory, and executive functioning) improved in comparison to pre-ECT cognition, presumably related to resolution of psychiatric symptoms that impaired cognition.

The memory loss sometimes observed after ECT can be both anterograde and retrograde and has a temporal gradient, being more prominent around the time of treatment course and continuing several weeks after the ECT course (American Psychiatric Association Task Force on Electroconvulsive Therapy 2001; Sackeim *et al.* 2000). Delayed recall is more affected than immediate recall, verbal more so than visual, and unstructured (e.g., random word lists) more so than contextualized (e.g., story recall) (Semkovska and McLoughlin 2010). In most patients any anterograde or retrograde memory problems clear quickly after ECT, as demonstrated in two pivotal National Institute of Mental Health trials (Kellner *et al.* 2010; O'Connor *et al.* 2001).

In rare cases the retrograde memory loss can be significant and may extend to events that occurred years before the ECT. There is a specific vulnerability of episodic/autobiographical memory to the effects of ECT, although autobiographical memory is also impaired by depression itself, and two recent reviews pointed out several methodological shortcomings in measures of autobiographical memory used in most ECT research to date (Brakemeier *et al.* 2011; Semkovska and McLoughlin 2013).

Evidence indicates that the degree of amnesia and global cognitive impairment incurred acutely during a course of ECT is greater with bitemporal ECT than with unilateral ECT (Lisanby *et al.* 2000; Semkovska and McLoughlin 2010), although this was not supported by a randomized trial comparing RUL, bifrontal, and bitemporal ECT, which showed only transient cognitive side effects with no significant differences based on electrode placement (Kellner *et al.* 2010). Evidence also suggests that cognitive side effects increase with the number of treatments administered, frequency of administration, and stimulus intensity (Sackeim *et al.* 2000; Shapira *et al.* 2000), although not all reports support these latter points (Semkovska and McLoughlin 2010).

Some long-term data also do not indicate that these acute differences in cognition in studies of unilateral versus bilateral ECT persist when assessed weeks to months after an ECT course. Although unilateral ECT is associated with fewer memory problems, the cognitive deficits that occur show a dose relationship and increase as the stimulus dose is increased to 8-12 times the seizure threshold (McCall *et al.* 2000; Semkovska and McLoughlin 2010). Research comparing bilateral and unilateral ECT has not addressed whether RUL ECT given at a dose of 10-12 times the seizure threshold would cause more cognitive side effects than bilateral ECT given at a dose that is minimally above or 1.5 times the seizure threshold. Bilateral ECT in this context generally refers to bitemporal electrode placement, but in a metaanalysis of bifrontal ECT for depression, Dunne and McLoughlin (2012) reported less global cognitive impairment with bifrontal (vs. bitemporal) ECT, on par with the overall global cognitive and amnestic effects of RUL ECT.

The causes of the memory disturbance associated with ECT are multifactorial and probably include the effects of anesthetic drugs, electrode placement, stimulus waveform, generalized seizures, and electrical dose (Sackeim *et al.* 2007). Because cognitive effects associated with ECT are perhaps the primary (rational) barrier to more widespread use of a highly effective treatment modality, not surprisingly researchers have started to explore ways to prevent or lessen these effects. In keeping with the possible cholinergic mechanisms of action of ECT-induced cognitive effects, at least three trials of acetylcholinesterase inhibitors (medications approved for treatment of certain dementias) have been reported in the literature, all small in sample size but all indicating benefit for general cognitive or memory-related test scores when the medications were administered during the acute phase of ECT (Matthews *et al.* 2013; Prakash *et al.* 2006; Stryjer *et al.* 2012). None of the trials reported any serious adverse events with these medications, which is notable considering theoretical concerns that cholinesterase inhibitors could cause prolonged paralysis when given with the muscle paralytic succinylcholine, commonly used in ECT anesthesia, and concerns that these medications could prolong the bradycardia or asystole that may immediately follow the electrical dose administration. Nonpharmacological efforts to mitigate cognitive side effects may also prove useful. Choi *et al.* (2011) reported positive early feasibility during ECT of a cognitive remediation intervention adapted from use among patients with mesial temporal lobe epilepsy.

Treatment-Emergent Mania

Switching to mania during a course of ECT, particularly in patients with a history of bipolar disorder, is rare but can occur (Angst *et al.* 1992). Although there is no established treatment once ECT-induced mania occurs (Lee *et al.* 2014), the best clinical approach is to stop ECT, start mood stabilizers, and reconsider the treatment plan. The best preventive treatment is to ensure that patients with a history of mania are on mood stabilizers during their acute course of ECT.

As discussed above, lithium is associated with an increase in the risk of delirium and prolonged neuromuscular blockade (Zolezzi 2016); however, stopping lithium before ECT will increase the risk of switching to mania. The treating clinician must determine the best course, which could include holding the evening dose of lithium the night before ECT in order to lower the blood level of lithium, switching temporarily to another mood stabilizer, or maintaining the lithium and monitoring for evidence of delirium.

The anticonvulsants used to treat mania (e.g., valproic acid, carbamazepine, topiramate, and lamotrigine) can increase the seizure threshold and potentially result in missed or abortive seizures. The antiepileptic medications have been shown in a retrospective study to result in higher seizure thresholds, shorter motor seizures, an increase in the number of failed seizures, and an increase in the maximum charge and number of treatments received (Virupaksha *et al.* 2010). However, this same retrospective study showed comparable symptom improvement in patients on and off antiepileptic medication. Other studies have found no effect of anticonvulsant medications on the efficacy of ECT or clinical outcomes (Jahangard *et al.* 2012; Rakesh *et al.* 2017). Using the methods-of-limit titration schedule can account for the increase in the seizure threshold, and the medications can be held the night before the treatment to decrease their effect on the seizure threshold. Another consideration could be to substitute an antipsychotic medication, which would have negligible effect on the seizure threshold and provide antimanic prophylaxis.

Postictal Agitation

Postictal agitation (PIA) can be a significant problem, with the potential for causing injury to both the patient and the nursing staff caring for the patient (Augoustides *et al.* 2002). PIA is difficult to predict in an individual patient and must be differentiated from status epilepticus. PIA is distinguished by the random flailing movements of the patient, in contrast to the rhythmic convulsions of a seizure, and by the fact that the patient does not lose consciousness or demonstrate the fixed gaze of a patient experiencing a generalized tonic-clonic seizure.

Several strategies are used in treating PIA, and most involve intravenous access. Midazolam or methohexital will often sedate the patient and can be very effective. Additionally, propofol can be used to manage PIA (Tzabazis *et al.* 2013). Intravenous haloperidol has been associated with ventricular ectopy (Greene *et al.* 2000) and should be used only for patients with cardiac monitors. The intramuscular atypical antipsychotic medications can be effective, with a more benign cardiac profile. Dexmedetomidine has been used to treat PIA in severe cases (Bryson *et al.* 2013; Cohen and Stewart 2013; O'Brien *et al.* 2010).

Preventive measures can also be taken. First, the use of an oral disintegrating atypical antipsychotic medication such as olanzapine at least 10 minutes before ECT can be very effective and does not require administration of any additional liquids (Hermida *et al.* 2016). Second, current drug use should be reviewed. Lithium has been associated with PIA and prolonged seizures (el-Mallakh 1988; Jha *et al.* 1996; Sadananda *et al.* 2013; Sartorius *et al.* 2005) and can be discontinued throughout the ECT course if clinically feasible or withheld the night before and morning of ECT treatments. Use of the anesthetic agent etomidate is also associated with PIA (Freeman 2009). Additionally, carbidopa has been linked to postictal delirium and should be withheld the morning of ECT treatment (Nymeyer and Grossberg 1997).

PIA has been correlated with increased serum lactate levels, and some have argued that increasing the succinylcholine dose to decrease ictal muscle activity and subsequent rises in serum lactate levels can decrease PIA (Auriacombe *et al.* 2000). Another strategy may therefore be to increase the succinylcholine dose if any muscle movement is present during the seizure. However, care should be taken because another potential cause of PIA is the patient awakening from anesthesia with latent paralysis

of the respiratory muscles. Patients describe this as very frightening and may question continuing ECT.

Interictal Delirium

Interictal delirium develops during a course of ECT and persists on days when the patient does not receive a treatment. This side effect is observed primarily in older adults and increases in incidence with advancing age (Figiel *et al.* 1990). ECT-induced interictal delirium is associated with prolonged hospitalization and an increased risk of falls. Among older adults, additional risk factors for interictal delirium are Parkinson's disease, Alzheimer's disease, one or more cardiovascular risk factors, and preexisting structural changes in the caudate nucleus observed on brain scans. Patients who develop postictal confusion are likely to have greater retrograde amnesia in the weeks and months after ECT (Sobin *et al.* 1995).

The incidence of delirium during a course of ECT can vary dramatically depending on the ECT technique used. As a rule, ECT-induced interictal delirium is a short-lived, reversible side effect if identified early. Once it has been identified, ECT treatments should be withheld until the delirium resolves. Subsequent treatments should be administered less frequently or at a lower electrical charge.

Effects of Electroconvulsive Therapy on Cerebral Physiology

Immediately after an ECT treatment, the EEG shows generalized slowing of brain wave activity. This slowing tends to increase and persist longer after successive treatments. After a course of ECT is completed, slow-wave activity gradually decreases, and EEGs show a reversion to baseline activity within 3 months (Weiner *et al.* 1986a). Rarely, electroencephalographic abnormalities may persist for more than 3 months. Prior electroencephalographic abnormalities may increase the risk for developing prolonged abnormalities after ECT, but the clinical significance of these abnormalities is unknown. Functional neuroimaging studies are consistent with post-ECT EEG findings of generalized slowing, especially in prefrontal regions. There is evidence from several studies of decreased cerebral perfusion and metabolism in frontal regions as well as decreased frontal connectivity with subcortical regions after a course of ECT (Abbott *et al.* 2014a); some postulate this is a possible mechanism of action for antidepressant effects of ECT, that is, quelling the "hyperconnectivity" that has been reported in frontal-subcortical circuits in MDD (Bolwig 2014).

Does Electroconvulsive Therapy Cause Brain Damage?

Human autopsy studies of patients who have received ECT have shown no convincing evidence of irreversible brain damage when ECT was administered with current techniques (Devanand *et al.* 1994; Oltedal *et al.* 2015; Scalia *et al.* 2007; Weiner 1984). These findings are supported by a brain MRI study in which no significant structural brain changes were found immediately or 6 months after the completion of ECT (Coffey *et al.* 1991). In a study of six depressed patients, cerebrospinal fluid markers of neuronal/glial degeneration (tau protein, neurofilament, and S-100 beta protein) were measured before and after a successful course of ECT and showed no biochemical evidence of neuronal/glial damage or blood-brain barrier dysfunction (Zachrisson *et al.* 2000). In fact, emerging evidence supports quite the opposite of these commonly held beliefs and fears among the public. ECS in animal studies has been associated with increased neurogenesis, synaptogenesis, angiogenesis, and gliogenesis, particularly in the hippocampus (Bouckaert *et al.* 2014). Human structural neuroimaging studies have revealed increased gray matter volume and increased hippocampal and amygdala volumes (Oltedal *et al.* 2017), increased volumes in frontolimbic areas (Gbyl and Videbech 2018), increased chemical markers of neurogenesis (Abbott *et al.* 2014b), and increased neuroplasticity (Bouckaert *et al.* 2014).

Prophylactic Somatic Treatment After Acute Response to Electroconvulsive Therapy

Although the short-term therapeutic benefits of ECT are clearly established, the 6-month relapse rate after ECT to treat depression remains high (Bourgon and Kellner 2000). Sackeim *et al.* (1990) followed 58 patients for 1 year after ECT and found a differential relapse rate of 64% in those with MDD (with and without psychotic features) in whom an adequate pre-ECT medication trial had failed. In contrast, the relapse rate in patients who did not receive an adequate pre-ECT antidepressant trial was only 32%. Other clinical and demographic factors, including the presence of delusions, were not significant in predicting relapse. The adequacy of the post-ECT maintenance medication did not correlate with relapse rates. However, post-ECT maintenance medications were not standardized, and the evaluation of the pre-ECT medication trial was retrospective. The conclusion of this study is intuitively appealing: Patients whose symptoms do not respond to antidepressant medication before ECT are those most likely to relapse with maintenance medication. With relapse occurring in almost two-thirds of such patients within 1 year after ECT, the relapse rate is alarmingly high.

In a prospective, randomized, double-blind trial, Sackeim *et al.* (2001) compared three maintenance strategies: placebo, nortriptyline (target steady-state level, 75-125 ng/mL), and nortriptyline plus lithium (target lithium steady-state level, 0.5-0.9 mEq/L). Over the 24-week trial, the depression relapse rate was 84% with placebo, 60% with nortriptyline, and 39% with nortriptyline plus lithium, indicating a statistically significant advantage for combination therapy. In another prospective study, Shapira *et al.* (1995) found that patients who responded to an acute course of ECT and subsequently underwent maintenance therapy with lithium for 6 months had a relapse rate of only 36%. Of the 22 patients in that study, the 8 who relapsed did so in the first 13 weeks. Several clinical factors were associated with relapse; these included a shorter duration of the index depressive episode, an additional depressive episode in the 12 months before ECT, and, again, failure of an adequate trial of antidepressant therapy before the ECT course.

The high relapse rates of depression in patients receiving antidepressant medications after a successful course of ECT have led clinicians to use alternative therapies, such as continuation or maintenance ECT, for patients who are at high risk for recurrence of their mood disorder. Continuation ECT is defined as ECT for up to 6 months after the acute ECT course (i.e., aimed at relapse prevention). Continuation ECT is differentiated from maintenance ECT, which is defined as ECT that continues for more than 6 months after the initial course (i.e., aimed at recurrence prevention).

The term *prophylactic ECT* is used to refer to any ECT treatments given as continuation or maintenance therapy. According to clinical guidelines, candidates for prophylactic ECT include individuals who have recurring affective episodes that are responsive to ECT and individuals who are resistant to, intolerant of, or noncompliant with antidepressant medications (American Psychiatric Association Task Force on Electroconvulsive Therapy 2001). The debate over appropriate prophylactic treatment for patients with an acute response to ECT has focused on the clinical decision to either continue therapy with antidepressant medications or initiate maintenance ECT.

The pivotal study in understanding this debate compared continuation pharmacology with nortriptyline and lithium to continuation ECT in 201 patients who had remitted with an acute course of bilateral ECT (Kellner *et al.* 2006). There was no statistical difference in the relapse rates, and more than half the patients in each group relapsed. This study demonstrates the high relapse rates after an acute course of ECT even with an aggressive pharmacological approach; however, the relapse rates in both groups were significantly lower than the relapse of patients in other studies on placebo controls. A metaanalysis suggested there was a modest efficacy of maintenance ECT with pharmacotherapy over pharmacotherapy alone (Elias *et al.* 2018).

The Prolonging Remission in Depressed Elderly (PRIDE) study evaluated the efficacy and tolerability of continuation ECT plus medication compared with medication alone in depressed geriatric patients after a successful course of ECT (Kellner *et al.* 2016a). This study demonstrated that tapering ECT after a successful acute course is effective in decreasing relapse after ECT.

A consensus conference from 2017 (Gill and Kellner 2019) summarized the evidence-based recommendations for maintenance treatment from the available data:

- The frequency of ECT sessions should be tapered after the patient responds to the acute course rather than stopped after they meet remission criteria.
- Electrode placement and pulse width during maintenance ECT should be the same as for the acute course. However, if a patient has an incomplete response, they may benefit from a more aggressive treatment during maintenance ECT if they show signs of relapse.
- Maintenance ECT should be combined with pharmacotherapy. Patients should be started on an antidepressant after an acute ECT course, and the maintenance antidepressant with the most data to support efficacy after ECT is nortriptyline, but venlafaxine is a good alternative. The antidepressant should not be one that had previously failed, which generally includes the antidepressants patients were on when they began their acute course of ECT.
- There is considerable evidence for the efficacy of lithium after ECT. Lithium augmentation is warranted if the patient has a history of treatment-refractory depression, bipolar disorder, bipolar diathesis (i.e., family history, atypical depression, hypomanic symptoms), psychotic depression, or significant suicidal risk or response, but not remission, to ECT. Lithium can be difficult to use while a patient is getting ECT because of the potential complication of lithium-induced delirium; however, patients can hold their dose of lithium before the ECT session to limit this potential side effect.
- The frequency of maintenance ECT should be individualized: "It is preferable to use a gradually decreasing frequency rather than a fixed frequency when commencing [maintenance ECT] for the first time for a patient, so as to find the lowest frequency at which that patient can remain well." Patients can be

"rescued" with additional ECT sessions when they show signs of relapse.

Investigational Procedures in Convulsive Therapies

A number of neuromodulation procedures are being investigated in mood disorders. These procedures exert their therapeutic effect by depolarizing neurons and initiating action potentials or modulating cell firing rates, resulting in the induction of neuroplastic changes in neural networks (Rossini *et al.* 2015). Three of these procedures are convulsive: iLAST dosing therapy, MST, and FEAST. These procedures are designed to induce seizures with more focal stimulation of the cortex than ECT and potentially produce a therapeutic seizure with fewer cognitive side effects.

iLAST involves titrating the seizure dose by adjusting the current amplitude to determine the seizure threshold (Radman and Lisanby 2017). This technique decreases the neuroanatomic area of the seizure and therefore decreases the spread of the seizure to cognitively sensitive brain structures such as the amygdala and hippocampus. Typically the seizure threshold titration procedure keeps the current amplitude constant at 800-900 mA and adjusts the frequency (or seizure length) to determine the seizure threshold. The iLAST technique is based on the fact that the electric field strength of 800-to 900-mA amplitude is significantly above what is required to induce a seizure and produces a nonfocal seizure that potentially increases cognitive side effects (Deng *et al.* 2011).

MST uses high-intensity, rapidly fluxed magnetic fields to produce seizure-inducing electrical currents in the brain. MST delivers a very-high-frequency stimulus (e.g., 100 Hz) that results in an electrical field that is more focal and superficial than ECT (Deng *et al.* 2011). The stimulus has less of a direct effect on the mesial temporal structures (e.g., hippocampus) and theoretically is associated with fewer cognitive side effects than ECT. To date, there are only small nonrandomized trials evaluating the efficacy of MST. MST was shown to be equivalent to ECT in one study (Kayser *et al.* 2011), although another study showed a less robust response (Fitzgerald *et al.* 2013). MST's cognitive safety has been either equivalent to (Fitzgerald *et al.* 2013; Kayser *et al.* 2011) or better than that of ECT (Lisanby *et al.* 2003; Polster *et al.* 2015).

The electrical stimulus used in FEAST technology induces more focal seizures in the prefrontal cortex by changing the ECT bipolar pulse to a monopolar pulse through use of a smaller anode (positive electrode) placed frontally and a larger cathode (negative electrode) on the vertex (Nahas *et al.* 2013). A SPECT scan of a patient undergoing FEAST demonstrated increases in regional cerebral blood flow that were limited to the right prefrontal cortex and postictal changes that generalized bilaterally (Chahine *et al.* 2014). A small open-label study supported an antidepressant effect (Nahas *et al.* 2013); however, future studies are needed to support this novel approach to convulsive therapy.

Conclusion

Nearly 80 years have passed since ECT was first used in the treatment of psychiatric disorders. The scientific evidence for the safety and efficacy of ECT has grown exponentially, and no available medical treatment is as effective in treating debilitating, life-threatening illnesses in a number of psychiatric disorders, including treatment-resistant depression, mania, catatonia, and schizophrenia. Other neuromodulation techniques, both convulsive and subconvulsive, hold promise for elucidating neuroanatomic pathways and increasing the available treatments for mood disorders. Further research is needed to elucidate which biomarkers and patient variables are associated with response to each of these treatments. However, for patients with severe, treatment-resistant mood disorders and schizophrenia, ECT remains the gold standard.

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CHAPTER 47

Psychedelic Drugs as Treatments in Psychiatry

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Over the past 20 years there has been a resurgence of interest in the therapeutic potential of several classes of currently illegal drugs, particularly serotonergic psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and dimethyl tryptamine (DMT) plus the entactogen 3,4-methylenedioxymethamphetamine (MDMA) (Nutt *et al.* 2020). The psychedelics are natural or seminatural molecules that are agonists of the serotonin type $_{2A}$ (5-HT$_{2A}$) receptor. In the 1950s and 1960s some were used therapeutically in psychiatry with a huge investment from National Institutes of Health that led to many hundreds of publications on LSD and a lower but still significant number on psilocybin.

They were used to treat a range of "neurotic" disorders, especially anxiety and depression, and some substance use disorders. Dosing took two forms: a high-single-dose treatment that produced a trip from which the person might emerge with a very different mindset (psychedelic therapy) and a lower dose that was used before each psychotherapy session to help break down the patient's resistance to engaging with their issues (psycholytic therapy). Clinical results from both treatment modalities were seen as generally very powerful and effective, with a low level of adverse effects. Problems such as psychosis and suicidality were rare, probably lower than in the populations treated with other approaches or left untreated (Passie *et al.* 2008).

The best-known results in treating substance use disorders came from the work of Bill Wilson (the founder of Alcoholics Anonymous), who said he escaped from the chains of his addiction as a result of a trip. Wilson's own experience led him to promote the use of LSD in the treatment of alcohol use disorder, and six trials were conducted before the drug was banned. A modern meta-analysis of these data by Krebs and Johansen (2012) found LSD to be more efficacious than any current therapy.

LSD, psilocybin, and most chemically related serotonergic agonist compounds were banned in the late 1960s. They were all put into Schedule I and so defined as having no accepted medical value and but significant potential for harm and dependence. This scheduling stopped research on psychedelics for over 40 years, and only in the past decade have attempts been made to reverse this scheduling. Because of their illegal status and because the National Institutes of Health stopped funding studies, research with these compounds nearly disappeared. In the current century, a few psychotherapy studies and human neuroimaging research on brain mechanisms have revealed the effects of these compounds on the brain, especially in regions that are thought to underpin depression, and these findings have led to a resurgence in interest and investment. (Note: Ketamine can have psychedelic effects, but its pharmacological target is glutamate [see Chapter 21, "Ketamine and Esketamine"].)

MDMA is a synthetic molecule, related to methamphetamine, that in the 1970s was synthesized and tested by Alexander Shulgin, who reported it as having special pro-empathy (entactogenic) properties. For this reason, psychotherapists on the West Coast of the United States began using MDMA, especially in couples counseling, where its entactogenic effects allowed couples to reexperience the affection that was present at the start of their involvement and to rebuild a failing relationship. At that time, MDMA was called Empathy and was legal (whereas many other amphetamine derivatives were already illegal), and this status gave rise to its recreational use in clubs and raves, under the name Ecstasy. A media and political backlash resulted, and the ensuing pressure led to MDMA being banned and treatment with Empathy being stopped.

Drugs Used in Psychedelic Trials

Almost all modern clinical research has been conducted with psilocybin, the active ingredient of magic mushrooms. In the body it is converted to psilocin, a 5-HT_{2A} receptor agonist that mediates its mind-altering properties. Its effects are rarely overwhelming, so they are somewhat easier to cope with than those of LSD or DMT. The effects of psilocybin taken orally last 4-6 hours, whereas those of LSD can last 12 hours or more, necessitating overnight stays for study participants.

DMT, when in its pure form, has to be given intravenously (or smoked) and has an effect lasting just a few minutes, which may not be long enough for useful therapeutic insights to develop. However, the intravenous infusion of the DMT can be extended to make the drug delivery and the associated psychedelic experience last longer, which could carry value. DMT is also used in the form of ayahuasca, a drink that is legal in a number of countries in Central and South America for religious and healing purposes. Ayahuasca contains two important plant products, one of which is DMT. The other is harmaline, a monoamine oxidase inhibitor that blocks this enzyme in gut and liver and so allows the DMT in the drink to get to the brain. Human neuroimaging studies of ayahuasca have shown it to have effects similar to those of psilocybin and LSD, and several open clinical trials using ayahuasca have been conducted in patients with depression. However, Western medicine has not yet adopted ayahuasca because its plant ingredient concentrations are hard to control, and the coadministration of a monoamine oxidase inhibitor is risky for some individuals (e.g., those on selective serotonin reuptake inhibitors [SSRIs]). To overcome these problems, several pharmaceutical companies are developing infusions of synthetic DMT. Also, the related compound 5-methoxy-N,N-dimethyltryptamine, a powerful short-acting psychedelic, is being developed for clinical evaluation, as are synthetic analogs of both psilocybin and LSD.

Ibogaine is a plant alkaloid from West Africa that is used in a number of countries as an unlicensed treatment for substance use disorders, especially those involving heroin, although there are no high-quality studies. Some deaths have been reported, probably due to QTc prolongation. This cardiac effect has limited research, and its effects on the brain are not yet characterized. An active metabolite, nor-ibogaine, is being developed as a possibly safer alternative.

Twenty-First-Century Resurrection of Psychedelics and MDMA in Psychiatry

Psychedelics

Over the past two decades, research on psychedelics has restarted for two reasons: the discovery of their novel effects on the brain and positive findings from small exploratory clinical studies. Neuroimaging results of functional MRI and magnetoencephalography reveal a disruption of brain activity in many regions but particularly the default mode network and the subgenual cingulate cortex. Various successful treatments of depression--from electroconvulsive therapy and deep brain stimulation to antidepressant drugs, psychotherapy, and even placebo--have been associated with reductions in subgenual cingulate cortex activity, supporting the view that this region is a key node in driving depression (Zhou *et al.* 2017). Other functional MRI imaging studies have found the default mode network to be overactive in depression (Zhou *et al.* 2020).

The first modern clinical trial of any psychedelic was by Moreno *et al.* (2006), who gave nine subjects with treatment-resistant OCD up to four different dosages of psilocybin in an open-label design (Table 47-1). A few years later, Grob *et al.* (2011) conducted a double-blind, crossover study in which a moderate (0.2 mg/kg) dose of psilocybin and an active placebo (niacin 250 mg) were given to 12 patients with advanced-stage cancer diagnoses that had resulted in acute stress or anxiety disorders as defined by DSM-IV (American Psychiatric Association 1994).

TABLE 47-1. Psilocybin studies: depression and related disorders

Study	Study type	Target illness	*N*	Primary outcome measure(s)	Main result	Control condition(s)
Moreno *et al.* 2006	Open label, up to four	OCD	9	Y-BOCS	Two-thirds showing	Very low dose

Note. BDI = Beck Depression Inventory; GRID-Ham-D = 17-item GRID format of Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; Ham-A = Hamilton Anxiety Scale; MDD = major depressive disorder; QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology-Self-Report; TRD = treatment-resistant depression; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Study	Study type	Target illness	*N*	Primary outcome measure(s)	Main result	Control condition(s)
	doses (range: 0.1-0.3 mg/kg body weight)				[?] 50% decrease in Y-BOCS at 1 day. One patient still in remission at 6-month follow-up.	psilocybin (0.025 mg/kg of body weight)
Grob *et al.* 2011	Double-blind crossover, single dose, 0.2 mg/kg	Patients with advanced-stage cancer and anxiety	12	BDI	Significant BDI reduction at 1 month after treatment and at 6-month follow-up.	Niacin
Griffiths *et al.* 2016	Double-blind, single dose (range: 22-30 mg/70 kg)	Patients with life-threatening cancer and depression	51	GRID-Ham-D and Ham-A	High dose showed ~3x and 4x greater response (Ham-D and Ham-A) and remission (Ham-D)	Low-dose psilocybin (1-3 mg/70 kg)

Note. BDI = Beck Depression Inventory; GRID-Ham-D = 17-item GRID format of Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; Ham-A = Hamilton Anxiety Scale; MDD = major depressive disorder; QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology-Self-Report; TRD = treatment-resistant depression; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Study	Study type	Target illness	*N*	Primary outcome measure(s)	Main result	Control condition(s)
		and/or anxiety			at 5 weeks, respectively, vs. low dose.	
Ross *et al.* 2016	Double-blind, fixed dose, 0.3 mg/kg	Patients with life-threatening cancer and depression and/or anxiety	29	BDI	83% response vs. 14% in control group at 7 weeks.	Niacin
Carhart-Harris *et al.* 2016, 2017	Open label, single dose, 25 mg	TRD	20	QIDS-SR	Significant improvement up to final follow-up (6 months), maximum effect at 5 weeks.	None
Carhart-Harris *et al.* 2021	Two 25-mg doses given 3	MDD	59	QIDS-SR	No significant difference	Low-dose psilocybin (1

Note. BDI = Beck Depression Inventory; GRID-Ham-D = 17-item GRID format of Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; Ham-A = Hamilton Anxiety Scale; MDD = major depressive disorder; QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology-Self-Report; TRD = treatment-resistant depression; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Study	**Study type**	**Target illness**	***N***	**Primary outcome measure(s)**	**Main result**	**Control condition(s)**
	weeks apart vs. 6 weeks of daily oral escitalopram (10 mg for 3 weeks; 20 mg for 3 weeks)				between groups in QIDS-SR response at 6 weeks. Most other outcomes favored psilocybin. Remission at 6 weeks: 57% in psilocybin group vs. 28% in escitalopram group (see Figure 47-1).	mg) or placebo capsules
Davis *et al.* 2021; Gukasyan *et al.* 2022	Two doses (20 mg and 30 mg/70 kg, respectively), with delayed	MDD	27	GRID-Ham-D	Large effect sizes at 5 weeks and 8 weeks; 54% and 58% in remission	Waiting list control

Note. BDI = Beck Depression Inventory; GRID-Ham-D = 17-item GRID format of Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; Ham-A = Hamilton Anxiety Scale; MDD = major depressive disorder; QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology-Self-Report; TRD = treatment-resistant depression; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Study	**Study type**	**Target illness**	***N***	**Primary outcome measure(s)**	**Main result**	**Control condition(s)**
	start for control group (*n* = 12)				at 4 weeks and 12 months, respectively.	
Goodwin *et al.* 2022	Multicenter double-blind, single dose, 25 mg vs. 10 mg	TRD	233	MADRS	Significant improvement and 25 mg superior to 1 mg at 3 weeks.	Low-dose psilocybin (1 mg)
von Rotz *et al.* 2023	Double-blind, single dose, 0.215 mg/kg	MDD	52	MADRS	Large effect sizes at 2 weeks, with 54% in remission.	Mannitol

Note. BDI = Beck Depression Inventory; GRID-Ham-D = 17-item GRID format of Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; Ham-A = Hamilton Anxiety Scale; MDD = major depressive disorder; QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology-Self-Report; TRD = treatment-resistant depression; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

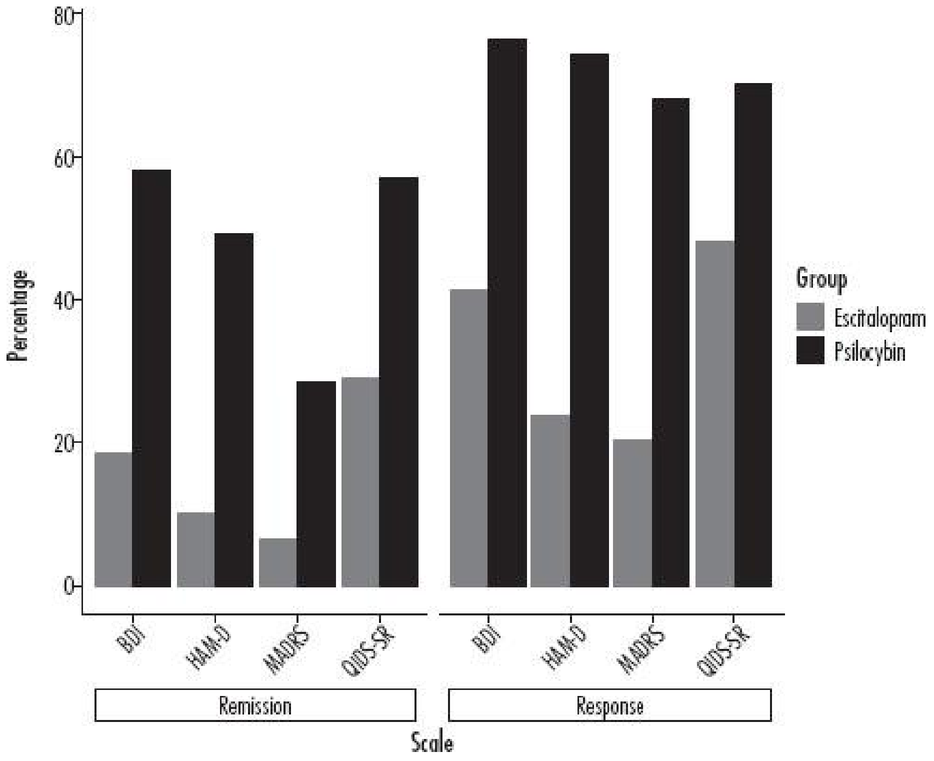

FIGURE 47-1. Response and remission rates for psilocybin versus escitalopram at week 6: comparative trial in 59 patients with long-standing depression.

See study description in text. Response (baseline to 6 weeks, all scales) was defined as > 50% reduction in scores. Remission (6 weeks) was defined as a QIDS-SR score of [?] 5, a BDI score of [?] 8, a MADRS score of < 10, and a Ham-D score of [?] 7. BDI = Beck Depression Inventory; Ham-D = 17-item Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology-Self-Report.

Source. Data from Carhart-Harris *et al.* 2021.

More recently, two studies of psilocybin in major depressive disorder (MDD) were conducted by the UK Imperial College team of Nutt and Carhart-Harris. In the first, an open-label study of patients with treatment-resistant depression, subjects were given first a low (10 mg test) and then a high (25 mg) oral dose of psilocybin (Carhart-Harris *et al.* 2016, 2017). In this study, patients had very-long-standing MDD (mean duration 17.7 years +- 8.4 years) that usually had been resistant to multiple treatments (mean number of failed medications: 4.6 +- 2.6). The primary outcome measure was the mean change in depression ratings on the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR). Highly significant improvements in QIDS-SR depression ratings were seen at all time points up to 6 months, with the maximal effect seen at 5 weeks (Cohen's *d* = 2.3).

Subsequently, the Imperial College group conducted a comparative trial of psilocybin versus the SSRI escitalopram in 59 patients with long-standing, moderate to severe MDD (Carhart-Harris *et al.* 2021). About half of the patients were weaned off antidepressants and half were drug-free. The psilocybin group (n = 30) received two 25-mg doses of psilocybin given 3 weeks apart plus 6 weeks of daily placebo, and the escitalopram group (n = 29) received two 1-mg doses of psilocybin given 3 weeks apart plus 6 weeks of daily oral escitalopram (10 mg daily for 3 weeks, then 20 mg for another 3 weeks). The primary outcomes were mood and well-being changes from baseline at 6 weeks. Well-being was significantly improved by both treatments, but was more improved with the high-dose (25 mg) psilocybin. Depression scores also improved with both treatments, and although the primary measure--change in QIDS-SR--did not differentiate the groups, all other mood measures favored psilocybin, as did the remission rates (Figure 47-1).

In the United States, Davis *et al.* (2021) conducted a psilocybin treatment study in MDD and found similar results. Twenty-seven patients underwent two psilocybin sessions (session 1, 20 mg/70 kg; session 2, 30 mg/70 kg) in the context of supportive psychotherapy. Depressive symptom ratings showed rapid decreases from baseline to day 1 after session 1 (from a mean [SD] QIDS-SR score of 16.7 [3.5] to 6.3 [4.4]; Cohen's d = 3.0), and ratings remained statistically significantly reduced through the week 4 follow-up.

In addition to Grob *et al.* (2011), there have been two other controlled studies of the use of psilocybin for anxiety and depression associated with life-threatening illness. In the United States, Griffiths *et al.* (2016) treated 51 patients with anxiety and depressive symptoms resulting from a life-threatening cancer diagnosis. Placebo was a very low (ineffective) dose of psilocybin (1 mg or 3 mg/70 kg) compared with the much higher active-treatment dose (22 mg or 30 mg/70 kg). Administration was counterbalanced with 5 weeks between sessions, and the study included a 6-month follow-up. The Hamilton Rating Scale for Depression (Ham-D) and the Hamilton Anxiety Scale were the primary outcome measures and showed superiority for the high dose versus the low dose at 5 weeks. The placebo group was then crossed over to a high dose, and these patients experienced significant improvements also.

Similarly, Ross *et al.* (2016) gave 29 patients with cancer-related anxiety and depression a single dose of 0.3 mg/kg psilocybin or 250 mg niacin as active placebo, with crossover at 7 weeks. The group receiving psilocybin showed clinical benefits, as measured by both clinician-and patient-rated scales, that lasted up to the crossover at 7 weeks and were then sustained for up to 8 months. The active-placebo group showed transient improvements, but these were not sustained, although these patients also showed immediate and sustained reductions in anxiety and depression scores after switching to psilocybin.

Another depression study was recently reported from Switzerland by von Rotz *et al.* (2023). It was a double-blind, randomized controlled trial (RCT) of 52 participants diagnosed with MDD who received either a single moderate dose (0.215 mg/kg body weight) of psilocybin or placebo in conjunction with psychological support. Two weeks after the intervention, participants in the psilocybin condition (*n* = 26) showed an absolute decrease in symptom severity of [?]13.0 points compared with baseline, which was significantly larger than the decrease seen in the placebo condition (*n* = 26). Among participants in the psilocybin condition, 14 of 26 (54%) met the MADRS remission criteria.

Additionally, in Switzerland, Gasser *et al.* (2015) performed a trial with LSD at either a low (20 mg) or a high (200 mg) dose for 10 patients with depression and trauma. The positive outcomes from this study led to this drug being made available for compassionate use in that country.

There have been several open trials of ayahuasca in depression, but the first RCT was conducted by Palhano-Fontes *et al.* (2019), who found a fast onset of effects and powerful reductions in depressive symptoms. In this study, 29 patients with moderate to severe treatment-resistant (Ham-D [?] 17) depression received either ayahuasca (0.36 mg/kg of DMT, *n* = 14) or placebo (a sour and bitter-tasting inert liquid, *n* = 15).

Building on the reports of the utility of psychedelics in alcohol use disorder from Wilson, the Johnson/Griffiths team at Johns Hopkins conducted an open study in which 15 people trying to stop smoking tobacco were treated with psilocybin 25 mg three times during a 20-week quitting course (Table 47-2). At 6 months, 12 of the 15 subjects had become smoking-free, and at 12 months, 10 of the 15 subjects remained smoking-free, a much better outcome than current smoking-cessation medicines (Johnson *et al.* 2017).

TABLE 47-2. Psilocybin studies: substance use disorders

Study	Study type	Target illness	*N*	Primary outcome measure(s)	Main result	Control condition(s)
Johnson *et al.* 2014, 2017	Open label, two fixed doses (20 and 30 mg/ 70 kg) and a third optional	Tobacco dependence	15	Abstinence	12 patients (80%) fully abstinent at 6 months, 10 at 12 months, and 9 at 30 months.	None
Bogenschutz *et al.* 2015	Open label, two or three fixed doses (0.3-0.4 mg/kg)	Alcohol dependence	10	Reduced heavy drinking days	Heavy drinking days significantly reduced during weeks 5-12 vs. baseline as well as vs. weeks 1-4.	None
Bogenschutz *et al.*	Double-blind,	Alcohol dependence	93	Reduced heavy	Reduction in heavy	Active placebo:

Note. DPH = diphenhydramine.

Study	Study type	Target illness	*N*	Primary outcome measure(s)	Main result	Control condition(s)
2022	two doses (25-40 mg/70 kg) in randomized phase. Offered single dose in open-label phase after 36 weeks.	nce		drinking days	drinking days during 32-week double-blind period significantly larger for psilocybin group vs. DPH group (23.6% vs. 9.7%).	DPH (50-100 mg)

Note. DPH = diphenhydramine.

Another study of psilocybin, involving 10 patients with DSM-IV-defined alcohol dependence, was conducted by Bogenschutz *et al.* (2015) at the University of New Mexico (see Table 47-2). Participants received two psilocybin treatments in addition to a standard psychotherapy course and demonstrated a marked reduction in heavy drinking days with psilocybin.

The Bogenschutz group recently reported a much larger double-blind RCT of two doses of psilocybin versus two doses of an active placebo, the antihistamine diphenhydramine (Bogenschutz *et al.* (2022). A total of 95 participants with alcohol use disorder were randomly assigned to psilocybin (*n* = 49) or diphenhydramine (*n* = 46). The main outcome measure was percentage of heavy drinking days during the 32-week double-blind period. Patients receiving psilocybin had a significantly lower percentage of heavy drinking days (9.7%) compared with those receiving diphenhydramine (23.6%), a mean difference of 13.9% (95% CI, 3.0-24.7; *P* = 0.01). Mean daily alcohol consumption (number of standard drinks per day) was also lower in the psilocybin group (see Table 47-2).

MDMA

Although MDMA is not a psychedelic in the traditional sense of the word, it does have profound effects that allow people insights into their psychiatric problems and has proved especially helpful in the treatment of PTSD (Table 47-3). Several studies run by the Multidisciplinary Association for Psychedelic Studies (MAPS) have demonstrated that a couple of sessions of exposure therapy under MDMA (usually 125 mg with a 62.5-mg booster after 2 hours) can have powerful therapeutic effects (Mithoefer *et al.* 2011, 2018). Based on these positive findings, both the FDA and European Medicines Agency gave their approval for multicenter studies in the United States and Europe, and the first of these was reported in 2021 (Mitchell *et al.* 2021). If the next one is similarly positive, then it seems likely that MDMA will also become an approved medicine sometime in the 2020s. In addition, preliminary UK data recently showed promise for MDMA-assisted therapy for the treatment of alcohol dependence (*n* = 14 [Sessa *et al.* 2021]) (see Table 47-3).

TABLE 47-3. MDMA studies: PTSD and alcohol use disorder

Study	**Study type**	**Target illness**	***N***	**Primary outcome measure(s)**	**Main result**	**Control condition(s)**
Six MAPS Phase II PTSD trials (Jerome *et al.* 2020), #12124	Double-blind RCTs; two doses (range: 75-125 mg)	PTSD	103	Reduced CAPS score	Majority of patients entered remission, symptom improvements continued at least 12 months after end of treatment.	Placebo/control doses (0-40 mg, *n* = 31)
MAPS Phase III trial	Double-blind RCT,	PTSD	90	Reduced CAPS score	Very large effect size at 2 months.	Placebo

Note. CAPS = Clinician-Administered PTSD Scale; MAPS = Multidisciplinary Association for Psychedelic Studies; RCT = randomized controlled trial.

Study	Study type	Target illness	*N*	Primary outcome measure(s)	Main result	Control condition(s)
(Mitchell *et al.* 2021), #11859	3 doses					
Sessa *et al.* 2021	Open label, two doses (187.5 mg)	Alcohol use disorder	14	Drinking level	Large reduction in drinking for up to 9 months in majority of patients.	Not applicable

Note. CAPS = Clinician-Administered PTSD Scale; MAPS = Multidisciplinary Association for Psychedelic Studies; RCT = randomized controlled trial.

Clinical Perspectives

Treatment with psychedelics and MDMA is more complex than conventional antidepressant or anti-addiction therapies, requiring psychotherapy with the administration of the drug. Many consider it a new form of treatment in psychiatry: drug-assisted psychotherapy (or psychotherapy-assisted drug treatment). Before being given the drug, patients need to be prepared for the powerful psychological experience of the psychedelic/MDMA session. This process involves at least one dedicated preparatory session with a trained therapist (often called a guide) in which the patient is educated about the rationale and procedure of the drug administration session and is reassured that they will be looked after throughout it.

The drug session itself is usually done in an environment that optimizes patient comfort and security, usually a pleasantly decorated and softly lit room as opposed to a traditional medical clinic. Patients are given eye-shades so they can better explore inner visual experiences, and in most studies music is available through headphones. At least one, and ideally two therapists or guides are present in the room for the trip duration (ideally one male and one female). They are there to provide reassurance and medical cover in case of a bad trip.

With psychedelic drug sessions, the therapists or guides talk with the patient only if the patient needs reassurance, which often they do not. It is important to note that there is no expectation of conversation during the trip and no direction of the patient's thinking by the therapists.

On the next day and subsequent days, in what are called integration sessions, the contents and experiences of the trip are discussed with the therapists who facilitate psychotherapeutic insights and behavior change. Often additional integration visits (typically two to four in total) are part of the study design. There is as yet no standard psychotherapeutic method for psychedelic therapy, but many groups use mindfulness-or acceptance-based therapies, such as Acceptance and Commitment Therapy (Hayes and Wilson 1994) or Watts's Accept, Connect, and Embody model (Watts and Luoma 2020).

An important difference between psychedelic-and MDMA-assisted therapy is that therapists or guides are more actively engaged during a therapeutic session with MDMA than with psychedelics, because therapeutic material, such as trauma, is discussed actively during the MDMA session.

Group treatment has some logistic benefits and is being used in some retreats that use ayahuasca for PTSD. Historically, LSD has been used effectively in group therapy, and the biotechnology company COMPASS Pathways has conducted group sessions with psilocybin to accelerate the training of therapists.

A major clinical issue relevant to the use of both psychedelics and MDMA is that the therapeutic effects are blunted in people taking SSRI antidepressants, probably through receptor desensitization. Similarly, their effects and hence efficacy are reduced in patients treated with 5-HT_{2A} receptor blocking drugs (e.g., antipsychotic drugs such as quetiapine and olanzapine and antidepressants such as mirtazapine). Therefore, to optimize therapeutic effects it is best to discontinue these medications before administering psychedelics or MDMA. But this needs to be done with care to reduce the risk of worsening the underlying depression or producing discontinuation reactions.

Duration of Action

For some patients the impact of just one or two dosing sessions can be very long-lasting (Andersen *et al.* 2021), allowing the prospect of a cure to be considered. For others the beneficial effects seem to wane over time, probably because the brain processes underlying these disorders, which are often decades old, have become deeply ingrained in the brain. For patients who experience relapse, follow-up treatments are now being explored, but the illegal status of these drugs in most countries makes their use outside clinical trials almost impossible, except in a few countries (e.g., Canada and Switzerland, where compassionate use is now allowed). In July 2023, regulators in Australia agreed to reschedule psilocybin and MDMA to make them available for

people with treatment-resistant depression and people with treatment-resistant PTSD, respectively (Therapeutic Goods Administration 2023).

Safety Concerns

Although the claims of harms that were used to justify the banning of psychedelics and MDMA were largely spurious, there is no question that the psychedelics have powerful effects on the mind and can take patients into challenging places relating to memories of past trauma. There is also the risk of precipitating or worsening psychosis (De Gregorio *et al.* 2016), and so these treatments are currently avoided in patients with a history of psychosis (and in first-degree family members); so far, patients with bipolar depression have not been treated in case mania might be induced. Note that if they are too challenging, the effects of psychedelics can be terminated with a benzodiazepine or an antipsychotic with 5-HT$_{2A}$ receptor blocking activity, such as risperidone or olanzapine.

Whereas the safety and potential neurotoxicity of recreational MDMA (Ecstasy) use has been controversial among scientists for decades, one-time or short-term use in the context of therapy is generally considered safe (Mitchell *et al.* 2021; Sessa *et al.* 2019). Acutely, an MDMA experience may include transient cognitive and executive deficits affecting verbal and spatial memory and processing speeds (Hanson and Luciana 2004). In addition, transient mild to moderate muscle tightness (especially of the jaw), decreased appetite, nausea, hyperhidrosis, and feeling cold have been reported in trials of MDMA-assisted therapy (Mitchell *et al.* 2021). When used recreationally, MDMA (but not psychedelics) has been associated with reversible (estimated to return to normal levels after about 200 days of abstinence) brain reductions of the serotonin reuptake transporter, but only among people who had used the drug more than about 50 times in their lives (Erritzoe *et al.* 2011). Importantly, recreational Ecstasy use often involves mixed use with other substances or impure samples of MDMA, which makes it hard to precisely estimate its harm outside a controlled lab or clinic setting. When ranked by experts with a range of other legal and illegal substances (including cannabis, heroin, and alcohol), Ecstasy is positioned at the less harmful end of the spectrum (Nutt *et al.* 2010; van Amsterdam *et al.* 2010, 2015). However, it is important to note that deaths attributed solely to recreational intake of MDMA have been reported (Schifano *et al.* 2003).

Brain Mechanisms

The current thinking with psychedelics (and perhaps MDMA also) is that they disrupt the maladaptive repetitive cognitive and behavioral circuits that underpin depression, PTSD, and substance use disorders. The trip itself may give patients a new view of a world without depression or addictive disorders and insights into the reasons for their illness that they can refute or reframe. Also, both psychedelics (Ly *et al.* 2020) and MDMA (Rozas *et al.* 2004) can increase neuroplasticity, which may facilitate psychotherapy and allow the brain to reset itself into a new, illness-free state.

There is growing evidence that the depression-lifting effects of psychedelics are mediated in quite a different way from those of antidepressant drugs such as the SSRIs. The SSRIs seem to protect against stress by enhancing serotonin function at the 5-HT$_{1A}$ receptor, thus making the patient more resilient (Carhart-Harris and Nutt 2017). Psychedelics acting via the 5-HT$_{2A}$ receptor are believed to reset the brain processes that underpin depressive thinking and so allow the patient to work through their issues and overcome their depression (Carhart-Harris and Nutt 2017).

MDMA works differently, as it releases serotonin by blocking (and even reversing) the action of the presynaptic serotonin reuptake transporter and also possesses some direct 5-HT$_2$ receptor agonism (Green *et al.* 2003). In addition, MDMA blocks tryptophan hydroxylase (i.e., inhibits synthesis of serotonin) (Schmidt and Taylor 1987) and increases cortisol, oxytocin, vasopressin, and dopamine levels (Colado *et al.* 2004; Parrott *et al.* 2008; Wolff *et al.* 2012). Functional MRI studies have located its main site of activity in the limbic system, where it suppresses activity especially of the amygdala and hippocampus (Carhart-Harris *et al.* 2015). It is believed that this damping down of the emotional memory circuits helps patients relive their traumas without being overwhelmed by the emotions that accompany these memories. The emotional responses can then be extinguished as the patient gets mastery of them (Nutt and de Wit 2021).

Microdosing

Microdosing is a term for the use of subpsychedelic and even subdetectable doses of psychedelics (not MDMA), usually 5%-10% of full psychedelic doses. Microdosing has become popular with people in the creative industries, who think it improves their creativity. Others claim it helps reduce stress, depression, and anxiety. Microdoses are taken regularly, usually a couple of times a week over months (Kuypers *et al.* 2019). However, because these drugs are illegal there is no way of knowing for sure what exactly is being taken. The best controlled trial so far used a novel "self-blinding" approach and found that the effect of LSD and psilocybin microdosing was probably mostly due to expectation (Szigeti *et al.* 2021). However, new, more controlled trials are being set up.

Future Directions and Research Needs

In the past few years there has been a massive expansion in research on psychedelics (and to a lesser extent MDMA) due to significant investments by companies that have been set up to develop these drugs as medicines. Controlled trials of psilocybin in other forms of depression, OCD, anorexia nervosa, and various substance-related and addictive disorders are under way, as well as some studies using LSD or DMT. But many key questions are still unresolved.

One question is the efficacy and safety of these drugs in other disorders, especially eating disorders (including anorexia nervosa and food addiction in obesity), chronic pain conditions (including fibromyalgia), and behavioral addictions (including gambling disorder). With an appropriate level of assisting therapy, disorders with the potential to benefit from psychedelics may also include difficult-to-treat conditions such as borderline personality disorder (also called emotionally unstable personality disorder) and depression in bipolar II disorder.

The optimal duration of the trip for therapeutic benefit is still uncertain and is the subject of ongoing research. One company is developing a 5-HT$_{2A}$ receptor antagonist to shorten the duration of therapeutic LSD trips. Another is exploring an intravenous infusion of DMT to increase the therapeutic duration. Others are exploring new routes such as nasal and buccal administration for DMT-like compounds. A related question is the extent to which psychotherapy is needed, because some people report clinical value when self-medicating.

An interesting neuroscientific question is whether the therapeutic activity of psychedelics can occur without a trip. Earlier work has shown that lower (subtrip) doses are less effective, but the complexity of the 5-HT$_{2A}$ receptor's postsynaptic messaging makes it possible to make agonists that activate the receptor without being psychedelic. Recent preclinical research has shown that it is possible to make 5-HT$_{2A}$ agonists that have antidepressant-like properties in rodents but do not produce the head twitch response, which in rodents is characteristic of drugs with psychedelic activity in humans. Time will tell whether or not they are psychedelic in humans and whether they are as effective as antidepressants as the classic psychedelics.

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        panic disorder, 507

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    - schizophrenia with agitation, 822
  - pharmacokinetics and disposition, 274, 816-817
  - side effects and toxicology, 748, 749, 773-774, 823-826
  - structure-activity relations, 814-815, 814
- Zolpidem, 282, 1054, 1158, 1163-1164, 1163, 1170, 1182-1183, 1186-1187
- Zonisamide, 280, 1052, 1118
- Zopiclone, 1163-1164, 1170
- Zuranolone, 648, 650-651, 652-653. *See also* Brexanolone and other neurosteroids

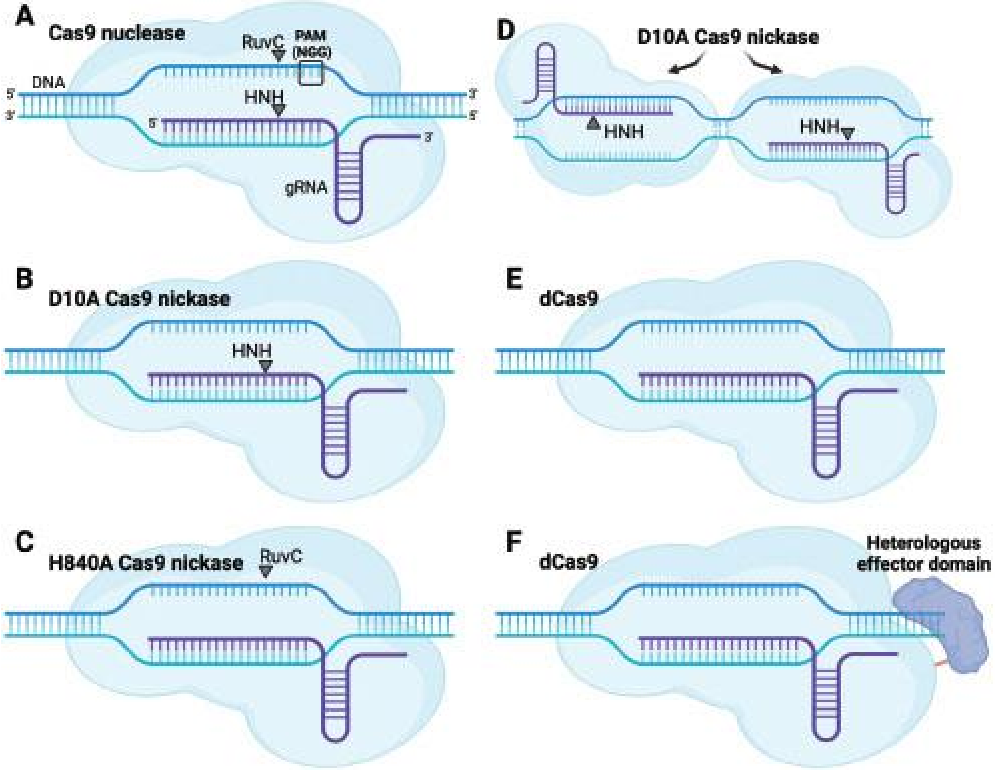

A
Cas9 nuclease
RuvC
PAM (NGG)
DNA
5'
3'
HNH
5'
3'
3'
5'
3'
gRNA
B
D10A Cas9 nickase
HNH
C
H840A Cas9 nickase
RuvC
D
D10A Cas9 nickase
HNH
HNH
E
dCas9
F
dCas9
Heterologous effector domain

PLATE 1. ***(Figure 1-7)*** **Cas9-based systems for altering gene sequence or expression.** **(A)** Cas9 nuclease creates double-stranded breaks at DNA target sites with complementarity to the 5' end of a gRNA. **(B)** Cas9 nickase created by mutation of the RuvC nuclease domain with a D10A mutation. This nickase cleaves only the DNA strand that is complementary to and recognized by the gRNA. **(C)** Cas9 nickase created by mutation of the HNH nuclease domain with an H840A mutation. This nickase cleaves only the DNA strand that does not interact with the small RNA. **(D)** Paired nickase strategy for improving Cas9 specificity. D10A Cas9 nickase directed by a pair of appropriately oriented gRNAs leads to induction of two nicks that, if introduced simultaneously, would be expected to generate a 5' overhang. **(E)** Catalytically inactive or "dead" Cas9 (dCas9) that can be recruited by a gRNA without cleaving the target DNA site. **(F)** Catalytically inactive dCas9-bearing dual D10A/H840A mutations fused to a heterologous effector domain. Cas9 = CRISPR-associated protein 9 nuclease from *Streptococcus pyogenes*; CRISPR = clustered regularly interspaced short palindromic repeat; gRNA = guide RNA; PAM (NGG) = protospacer adjacent motif (sequence 5'-NGG-3', where "N" is any nucleobase followed by two guanine ["G"] nucleobases).

Source. Created with BioRender.com.

PLATES 2 AND 3. ***(Figure 1-9)*** **Optogenetic manipulation of neural circuits** ***(opposite page).***

(I) Direct stimulation of neuronal cell bodies is achieved by injecting virus at the target region and then implanting a light-delivery device above the injected region. Even this simple experiment can provide specificity with viruses that will not transduce afferent axons and fibers of passage. **(II)** Additional cell-type specificity is attained either by cell-type-specific promoters in the viral vector or via a recombinase-dependent virus, injected in a transgenic animal expressing a recombinase such as Cre in specific cells, leading to specific expression of the transgene only in defined cell types. **(III)** Projection (axonal) targeting is achieved by viral injection at the region harboring cell bodies, followed by implantation of a light-delivery device above the target region containing neuronal processes from the virally transduced region; in this way, cell types are targeted by virtue of their projections. **(IV)** Projection termination labeling is a more refined version of projection targeting, in which cells are targeted by virtue of synaptic connectivity to the target region, with likely exclusion of cells whose axons simply pass through the region. Transcellular labeling using a recombinase-dependent system is shown. Viruses expressing Cre fused to a trans-neuronal tracer (lectin) are delivered at the synaptic target site, and a Cre-dependent virus is injected into the region with cell bodies. Cells that project to the Cre-injected area express the Cre-dependent virus and become light sensitive. Transcellular labeling can also be achieved with axon terminal-transducing viruses, although without control over the postsynaptic cell type. **(V)** Expression of two opsins with different characteristics in one brain region using a combination of promoter-or Cre-based approaches. Light delivery to the somata is performed using two different wavelengths designed to minimize cross-activation. **(VI)** Projections from two different brain regions are differentially stimulated with two wavelengths matched to the respective opsins expressed upstream.

Source. Adapted from Figure 2 (p. 18) in Yizhar O, Fenno LE, Davidson TJ, et al.: "Optogenetics in Neural Systems." *Neuron* 71(1):9-34, 2011 (https://doi.org/10.1016/j.neuron.2011.06.004). Copyright (c) 2011, Elsevier, Inc. Used with permission.

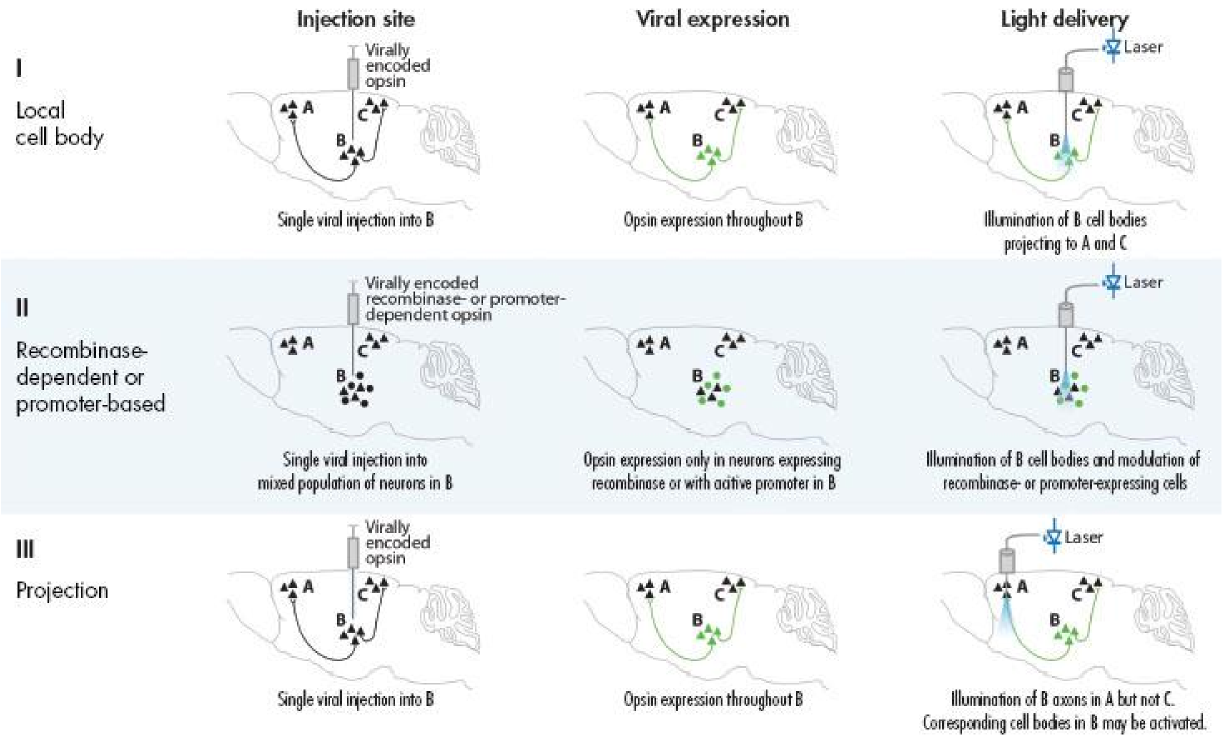

Injection site
Viral expression
Light delivery
I
Local cell body
Virally encoded opsin
A
B
C
Single viral injection into B
Opsin expression throughout B
Laser
Illumination of B cell bodies projecting to A and C
II
Recombinase-dependent or promoter-based
Virally encoded recombinase- or promoter-dependent opsin
Single viral injection into mixed population of neurons in B
Opsin expression only in neurons expressing recombinase or with active promoter in B
Illumination of B cell bodies and modulation of recombinase- or promoter-expressing cells
III
Projection
Virally encoded opsin
Single viral injection into B
Opsin expression throughout B
Illumination of B axons in A but not C. Corresponding cell bodies in B may be activated.

PLATE 2. Optogenetic manipulation of neural circuits *(continued).*

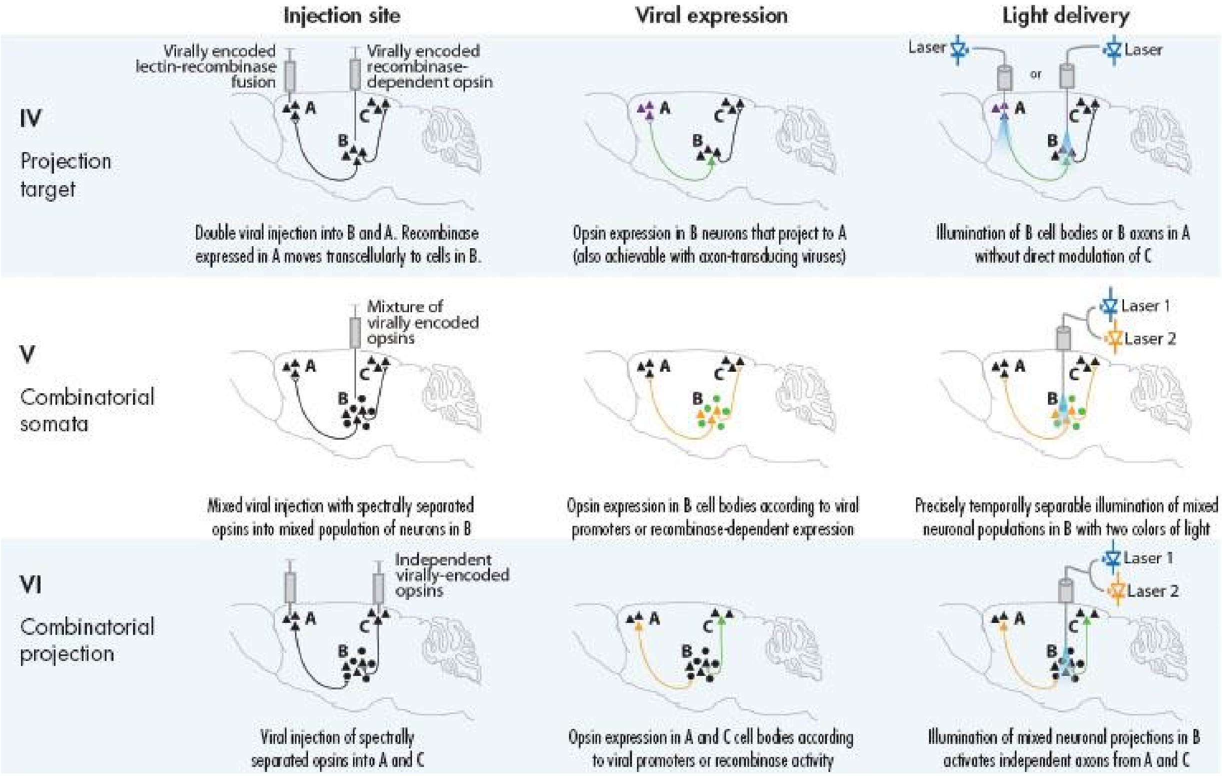

Injection site
Viral expression
Light delivery
IV
Projection target
Virally encoded lectin-recombinase fusion
Virally encoded recombinase-dependent opsin
A
B
C
Double viral injection into B and A. Recombinase expressed in A moves transcellularly to cells in B.
Opsin expression in B neurons that project to A (also achievable with axon-transducing viruses)
Laser
or
Illumination of B cell bodies or B axons in A without direct modulation of C
V
Combinatorial somata
Mixture of virally encoded opsins
Mixed viral injection with spectrally separated opsins into mixed population of neurons in B
Opsin expression in B cell bodies according to viral promoters or recombinase-dependent expression
Laser 1
Laser 2
Precisely temporally separable illumination of mixed neuronal populations in B with two colors of light
VI
Combinatorial projection
Independent virally-encoded opsins
Viral injection of spectrally separated opsins into A and C
Opsin expression in A and C cell bodies according to viral promoters or recombinase activity
Illumination of mixed neuronal projections in B activates independent axons from A and C

PLATE 3. Optogenetic manipulation of neural circuits *(continued).*

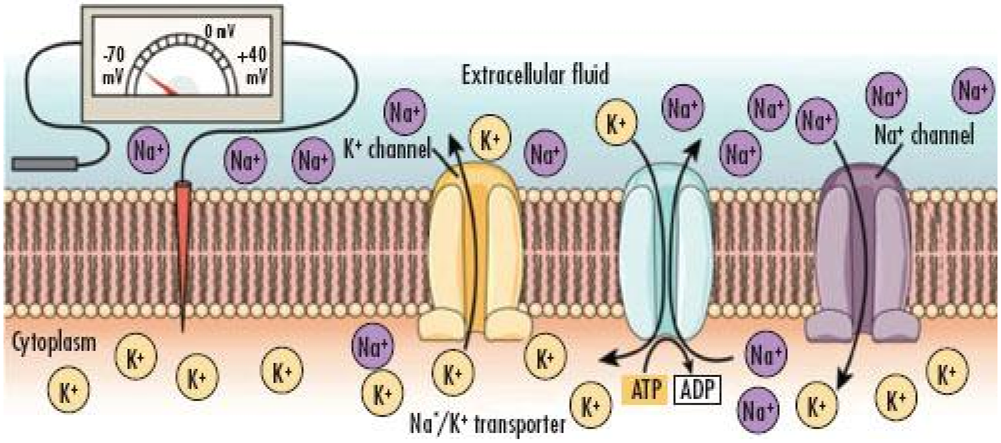

-70 mV
0 mV
+40 mV
Extracellular fluid
Na+
K+ channel
K+
Na+ channel
Cytoplasm
ATP
ADP
Na+/K+ transporter

PLATE 4. ***(Figure 2-2)*** **Ion channel function in the CNS.**

The plasma membrane Na$^+$/K$^+$ ATPase establishes a concentration gradient in the CNS, pumping Na$^+$ out and K$^+$ into the cell. Ion channels permit the passive diffusion of ions across the plasma membrane. Thus, opening of Na$^+$ channels depolarizes--and of K$^+$ channels hyperpolarizes--a neuron. ADP = adenosine diphosphate; ATP = adenosine triphosphate; mV = millivolt.

Source. Reprinted from Figure 35.10c (Hyperpolarization) in Biology 2e. Provided under a Creative Commons Attribution 4.0 license (CC BY 4.0) by OpenStax (https://openstax.org/books/biology-2e/pages/1-introduction).

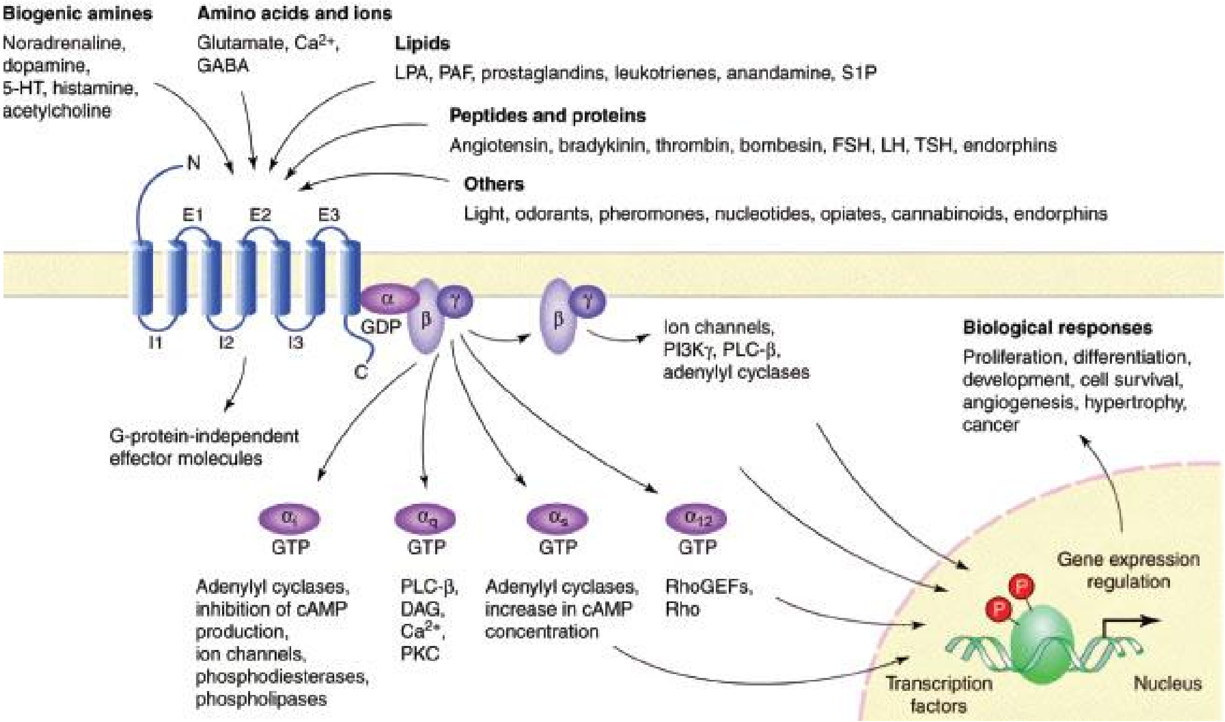

Biogenic amines
Noradrenaline, dopamine, 5-HT, histamine, acetylcholine
Amino acids and ions
Glutamate, Ca2+, GABA
Lipids
LPA, PAF, prostaglandins, leukotrienes, anandamine, S1P
Peptides and proteins
Angiotensin, bradykinin, thrombin, bombesin, FSH, LH, TSH, endorphins
Others
Light, odorants, pheromones, nucleotides, opiates, cannabinoids, endorphins
N
E1
E2
E3
I1
I2
I3
C
α
GDP
β
γ
β
γ
Ion channels, PI3Kγ, PLC-β, adenylyl cyclases
Biological responses
Proliferation, differentiation, development, cell survival, angiogenesis, hypertrophy, cancer
G-protein-independent effector molecules
αi
GTP
αq
GTP
αs
GTP
α12
GTP
Adenylyl cyclases, inhibition of cAMP production, ion channels, phosphodiesterases, phospholipases
PLC-β, DAG, Ca2+, PKC
Adenylyl cyclases, increase in cAMP concentration
RhoGEFs, Rho
Gene expression regulation
P
P
Transcription factors
Nucleus

PLATE 5. ***(Figure 2-4)*** **Diversity of G protein-coupled receptors (GPCRs) signaling.**

A wide variety of ligands, including biogenic amines, amino acids, ions, lipids, peptides, and proteins, use GPCRs to stimulate cytoplasmic and nuclear targets through heterotrimeric G-protein-dependent and -independent pathways. Such signaling pathways regulate key biological functions such as cell proliferation, cell survival, and angiogenesis. 5-HT = 5-hydroxytryptamine; C = carboxy terminus; cAMP = cyclic adenosine monophosphate; E1, E2, E3 = extracellular loop 1, 2, 3; DAG = diacylglycerol; FSH = follicle-stimulating hormone; GDP = guanosine diphosphate; GEF = guanine nucleotide exchange factor; GTP = guanosine triphosphate; I1, I2, I3 = intracellular loop 1, 2, 3; LH = luteinizing hormone; LPA = lysophosphatidic acid; N = amino terminus; P = phosphorus; PAF = platelet-activating factor; PI3K = phosphatidylinositol 3-kinase g; PKC = protein kinase C; PLC-b = phospholipase C-b; S1P = sphingosine-1-phosphate; TSH = thyroid-stimulating hormone.

Source. Reprinted from Figure 1 (p. 368) in Marinissen MJ, Gutkind JS: "G-Protein-Coupled Receptors and Signaling Networks: Emerging Paradigms." *Trends in Pharmacological Sciences* 22(7):368-376, 2001 (https://doi.org/10.1016/S0165-6147(00)01678-3). Copyright (c) 2001, Elsevier Science Ltd. Used with permission.

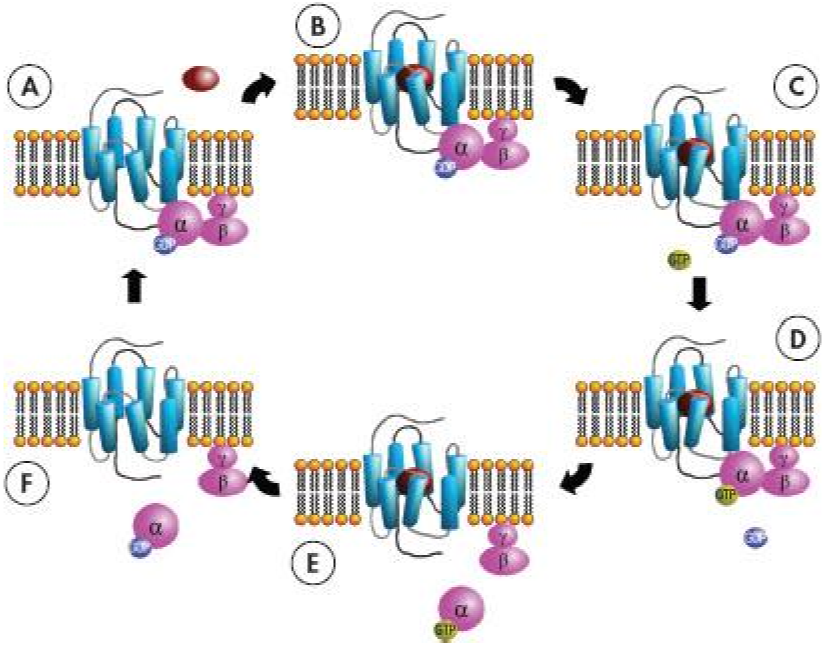


PLATE 6. ***(Figure 2-5)*** **G protein activation cycle.**

Source. By Sven Jahnichen. Creative Commons Attribution-ShareAlike 3.0 Unported; https://commons.wikimedia.org/w/index.php?curid=730049.

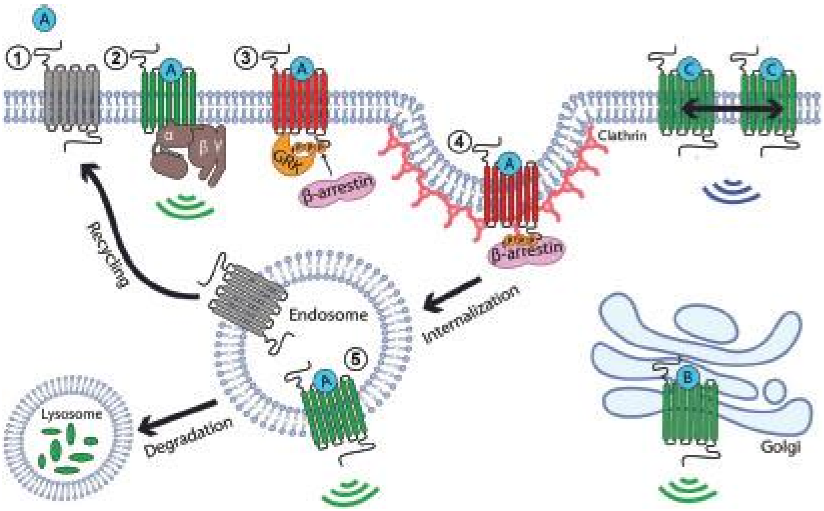


PLATE 7. ***(Figure 2-8)*** **Agonist-induced signaling and trafficking of opioid receptors.** Inactive opioid receptors (*gray*) become activated (*green*) after binding to an agonist (drug A; steps 1-2). The active receptor enables signaling via G proteins (*green ripples*, step 2) and triggers phosphorylation of the receptor tail (P) by G protein-coupled receptor kinases (GRKs), followed by receptor engagement of b-arrestins (step 3) and endocytosis via clathrin-coated pits (step 4). These events inactivate G protein signaling (*red receptor*) and ensure signal termination from the plasma membrane by endocytic removal of receptors. After receptors arrive in early endosomes, they have the capacity to signal again by engaging G proteins in the endosome membrane (*green ripples*, step 5). Receptors also engage molecular sorting mechanisms in the endosome limiting membrane (not shown), which determine whether internalized receptors are delivered to lysosomes for proteolytic downregulation or are nondestructively recycled to restore surface receptor responsiveness. Many nonpeptide agonist drugs (drug B) are sufficiently membrane-permeant to activate a discrete pool of opioid receptors at the Golgi apparatus and activate receptors from this location (*green ripples*). Some agonists (drug C) induce receptor reorganization in the plasma membrane to change surface signaling (*blue ripples*).

Source. Reprinted from Figure 1 (p. 426) in Jullie D, Gondin AB, von Zastrow M, Canals M: "Opioid Pharmacology Under the Microscope." *Molecular Pharmacology* 98:425-432, 2020 (https://doi.org/10.1124/mol.119.119321). Copyright (c) 2020, The American Society for Pharmacology and Experimental Therapeutics. Used with permission.

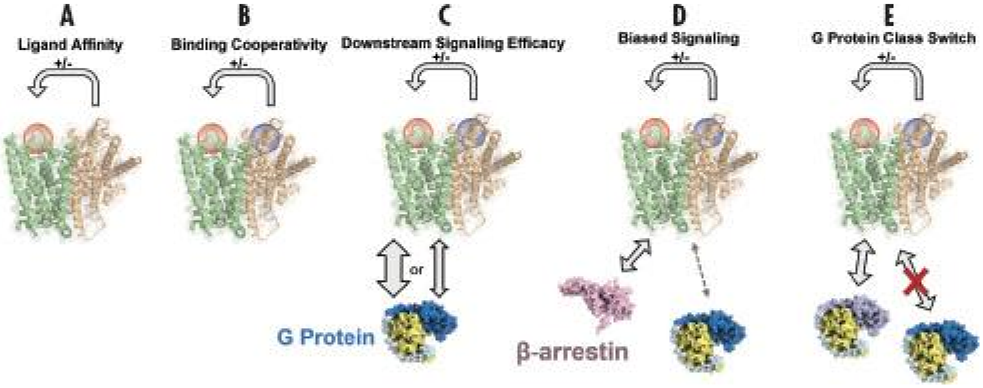


PLATE 8. ***(Figure 2-9)*** **Models of allosteric interactions between protomers of a heteromer.**

(A) The affinity of a ligand for one protomer (*green*) can be altered by the association of the second protomer (*blue*). **(B)** Binding of an orthosteric ligand to one protomer can alter the affinity of an orthosteric ligand for the second protomer. **(C)** Binding of an orthosteric ligand to one protomer can change the signaling efficiency (intrinsic efficacy) of the orthosteric ligand for the second protomer. Shown is efficiency of coupling to a heterotrimeric G protein, but this extends to other signal-transducing molecules (e.g., b-arrestin). **(D)** Binding of an orthosteric ligand to one protomer can alter the efficiency of coupling of the receptor produced by orthosteric ligand binding to the second protomer to each of multiple transducer molecules (i.e., can alter functional selectivity or agonist bias). Shown are alterations in coupling to a G protein versus b-arrestin. **(E)** Orthosteric ligand binding to one protomer can cause a change in the G protein-coupling specificity produced by the orthosteric ligand for the second protomer (this also changes agonist bias). Shown is a change in coupling efficiency to G proteins with two different a subunits (*light vs. dark blue*).

Source. Modified from Figure 3 (p. 225) in Botta J, Appelhans J, McCormick PJ: "Chapter 7-Continuing Challenges in Targeting Oligomeric GPCR-Based Drugs" (https://doi.org/10.1016/bs.pmbts.2019.11.009), in *Oligomerization in Health and Disease: From Enzymes to G Protein-Coupled Receptors*, Vol 169 (Progress in Molecular Biology and Translational Science book series). Edited by Giraldo J, Ciruela F. Cambridge, MA, Academic Press, 2020, pp. 213-245. Copyright (c) 2020, Elsevier Inc. Used with permission.

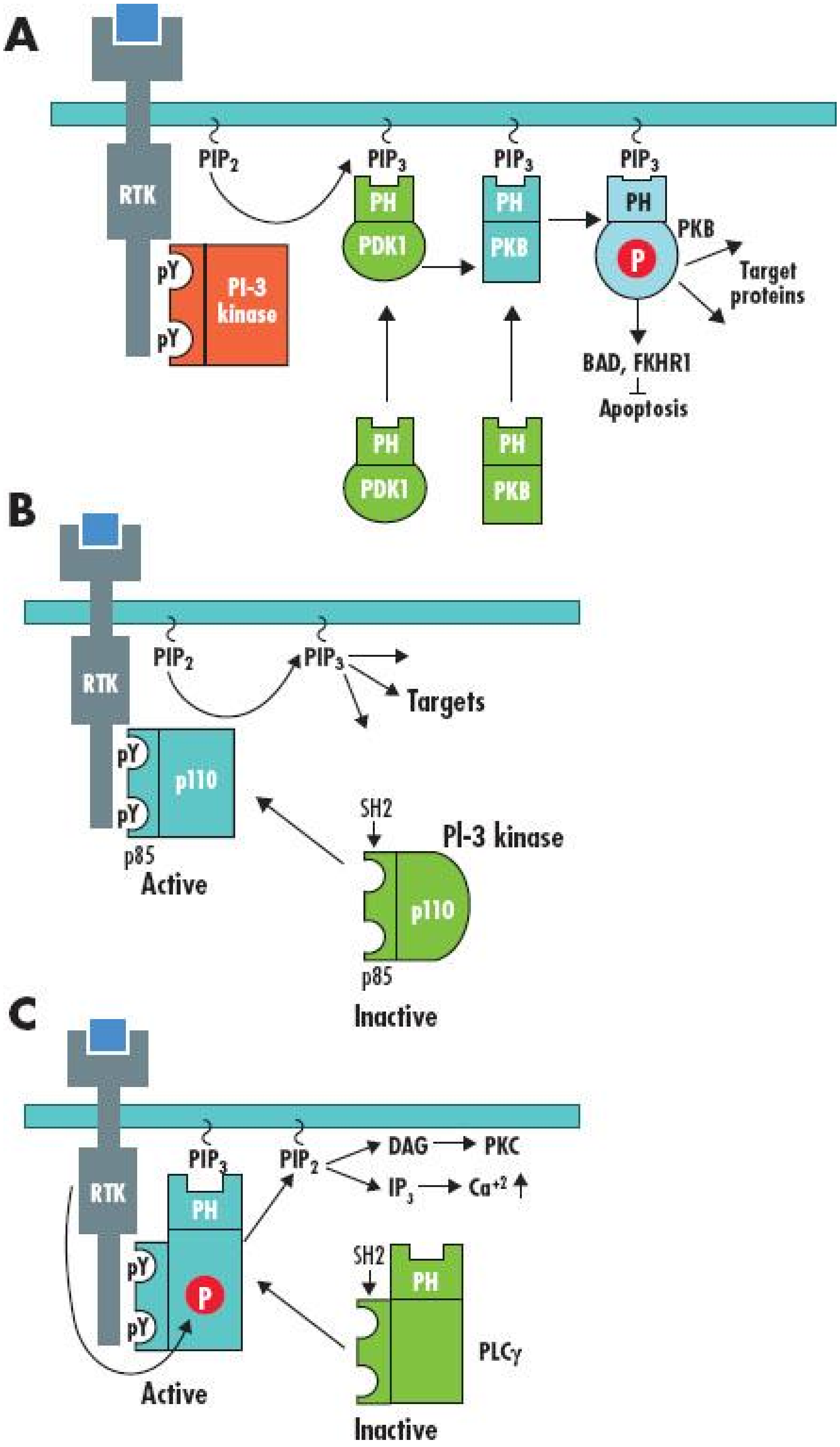

A
RTK
pY
pY
PI-3 kinase
PIP₂
PIP₃
PH
PDK1
PIP₃
PH
PKB
PIP₃
PH
PKB
P
Target proteins
BAD, FKHR1
Apoptosis
PH
PDK1
PH
PKB
B
RTK
PIP₂
PIP₃
Targets
pY
pY
p110
p85
Active
SH2
PI-3 kinase
p110
p85
Inactive
C
RTK
PIP₃
PH
PIP₂
DAG
PKC
IP₃
Ca⁺²
pY
pY
P
Active
SH2
PH
PLCγ
Inactive

PLATE 9. *(Figure 2-10)* Paradigms for activation of signaling proteins in response to receptor tyrosine kinase (RTK) activation.

At least two separate molecular events are required for RTK-induced activation of signaling molecules. Given that many protein targets of RTKs are located at the cell membrane, translocation of RTK to the cell membrane is essential for activation of many effector proteins. **(A) Activation of PKB (also known as Akt) by membrane translocation.** PtdIns(3,4,5)P3 generated in response to growth factor stimulation serves as a binding site for the PH domains of PDK1 and PKB. Membrane translocation is accompanied by release of an autoinhibition leading to activation of PDK1 and PKB kinase activities. Full activation of PKB requires phosphorylation by PDK1 (and also by PDK2). Activated PKB phosphorylates a variety of target proteins that prevent apoptotic death and regulate various metabolic processes. **(B) Activation by a conformational change.** Binding of the SH2 domains of p85, the regulatory subunit of PI-3 kinase, to pTyr sites on activated receptors releases an autoinhibitory constraint that stimulates the catalytic domain (p110). PI-3 kinase catalyzes the phosphorylation of the 39 positions of the inositol ring of PtdIns(4)P and PtdIns(4,5)P2 to generate PtdIns(3,4)P2 and PtdIns(3,4,5)P3, respectively. **(C) Activation by tyrosine phosphorylation.** Binding of the SH2 domains of PLCg to pTyr sites in activated receptors facilitates tyrosine phosphorylation of PLCg as well as membrane translocation, a process mediated in part by binding of the PH domain to PI-3 kinase products. Tyrosine phosphorylation is essential for PLCg activation, leading to hydrolysis of PtdIns(4,5)P2 and generation of the two second messengers Ins(1,4,5)P3 and diacyglycosol. BAD = Bcl-2 agonist of cell death; DAG = diacylglycerol; FKHR1 = winged helix transcription factor; Ins (1,4,5)P3 = inositol 1,4,5-trisphosphate; IP_3 = inositol 1,4,5-trisphosphate; p110 = catalytic subunit of PI-3 kinase; p85 = regulatory subunit of PI-3 kinase; PDK1 = pyruvate dehydrogenase kinase isoform 1; PDK2 = pyruvate dehydrogenase kinase isoform 2; PH = Pleckstrin homology; PI = phosphatidylinositol; PI-3 kinase = phosphatidylinositol-3 kinase; PIP_2 = phosphatidylinositol (4,5)-bisphosphate; PIP_3 = phosphatidylinositol (3,4,5)-trisphosphate; PKB = protein kinase B; PKC = protein kinase C; PLCg = phospholipase C gamma; PtdIns(3,4)P2 = phosphatidylinositol-bisphosphate; PtdIns(3,4,5)P3 = phosphatidylinositol (3,4,5)-trisphosphate; PtdIns(4)P = phosphatidylinositol-4-phosphate; PtdIns(4,5)P2 = phosphatidylinositol 4,5-bisphosphate; pY = phosphorylated tyrosine residue; pTyr = phosphotyrosine; SH2 = Src homology 2.

Source. Reprinted from Figure 4 (p. 216) in Schlessinger J: "Cell Signaling by Receptor Tyrosine Kinases." *Cell* 103(2):211-225, 2000 (https://doi.org/10.1016/S0092-8674(00)00114-8). Copyright (c) 2000, Cell Press. Used with permission.

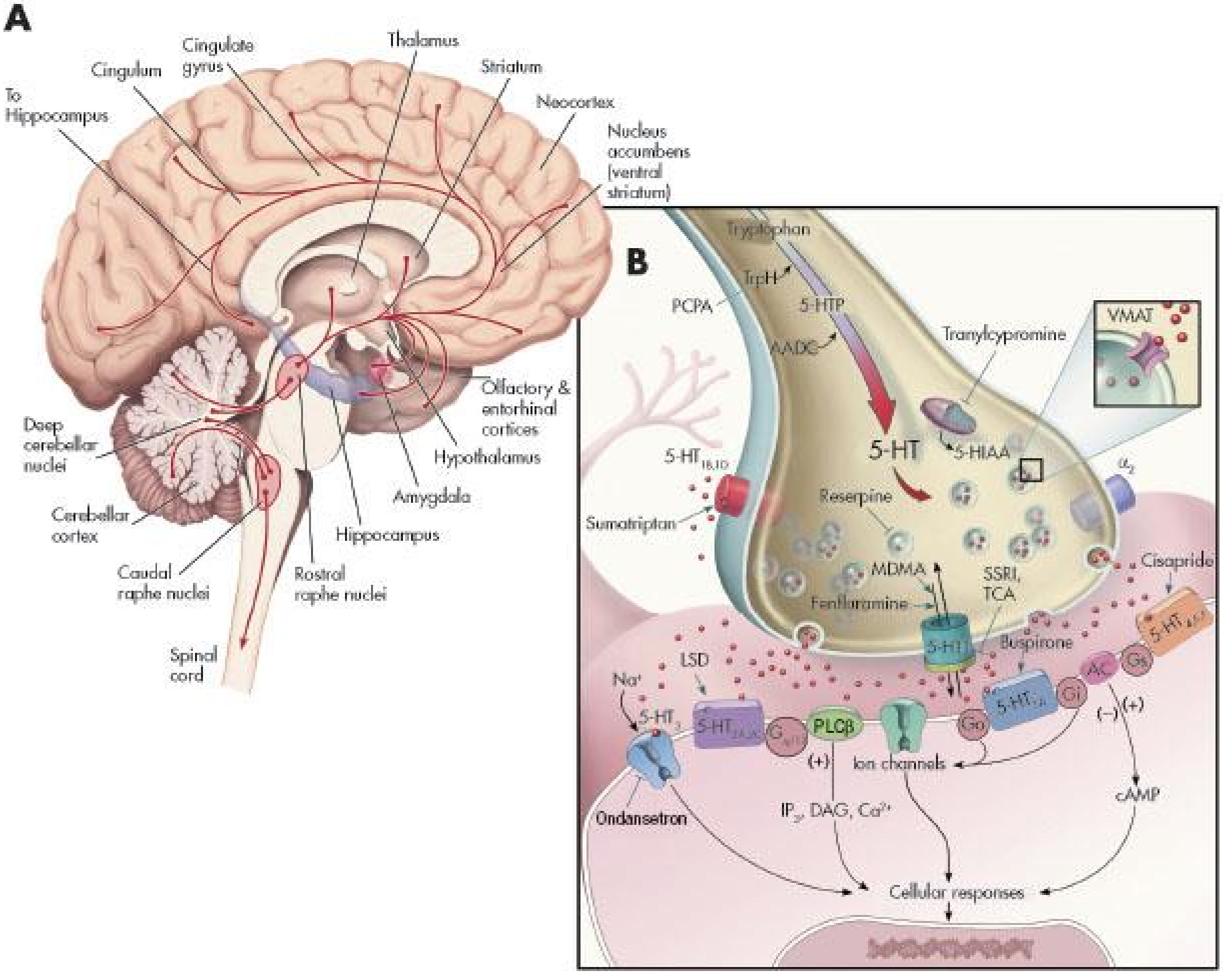

A
To Hippocampus
Cingulum
Cingulate gyrus
Thalamus
Striatum
Neocortex
Nucleus accumbens (ventral striatum)
Olfactory & entorhinal cortices
Hypothalamus
Amygdala
Hippocampus
Deep cerebellar nuclei
Cerebellar cortex
Caudal raphe nuclei
Rostral raphe nuclei
Spinal cord
B
Tryptophan
TrpH
PCPA
5-HTP
AADC
Tranylcypromine
VMAT
5-HT
5-HIAA
$5\text{-HT}_{1B,1D}$
Sumatriptan
Reserpine
α_2
MDMA
Fenfluramine
SSRI, TCA
Cisapride
5-HTT
Buspirone
$5\text{-HT}_{4,6,7}$
LSD
Na^+
5-HT_3
$5\text{-HT}_{2A,2C}$
$G_{q/11}$
PLCβ
Go
5-HT_{1A}
Gi
AC
Gs
(–)
(+)
(+)
Ion channels
cAMP
Ondansetron
IP_3, DAG, Ca^{2+}
Cellular responses

PLATE 10. ***(Figure 2-11)*** **The serotonergic system.**

(A) Location of the major serotonin (5-hydroxytryptamine [5-HT])-producing cells (raphe nuclei) innervating brain structures. **(B)** Various cellular regulatory processes involved in serotonergic neurotransmission and sites of action of drugs affecting serotonergic transmission. *L-Tryptophan*, the precursor for 5-HT, is converted to 5-hydroxytryptophan (5-HTP) by the rate-limiting enzyme tryptophan hydroxylase (TrpH). Aromatic L-amino acid decarboxylase (*AADC*) then converts 5-HTP to 5-HT. Once released from the presynaptic terminal, 5-HT can interact with a variety (14 different types) of presynaptic and postsynaptic receptors. *Sumatriptan*, a $5\text{-HT}_{1B,1D}$ receptor agonist, has antimigraine effects that are thought to be due to activation of $\text{HT}_{1B,1D}$ receptors expressed on smooth muscle (to produce vasoconstriction) and also on pain-sensing neurons (i.e., *nociceptors*) (to reduce the release of pain-related neuropeptides). *Buspirone* is a partial 5-HT_{1A} receptor agonist that activates both pre-and postsynaptic receptors. *Cisapride* is a preferential 5-HT_4 receptor agonist that is used to treat irritable bowel syndrome as well as nausea associated with antidepressants. Binding of 5-HT to G protein-coupled receptors (GPCRs) that are coupled to adenylyl cyclase (AC) and phospholipase C beta (PLCb) will result in production of a cascade of second-messenger and cellular effects. Lysergic acid diethylamide (*LSD*) likely interacts with numerous 5-HT receptors to mediate its effects. Pharmacologically, this ligand is often used as a 5-HT$_2$ receptor agonist in receptor-binding experiments. *Ondansetron* is a 5-HT$_3$ receptor antagonist that is marketed as an antiemetic agent for chemotherapy patients but is also given to counteract side effects produced by antidepressants in some patients. 5-HT has its action terminated by being taken back into the presynaptic neuron through 5-HT transporters (5-HTTs [also called SERTs]). (Note that 5-HTTs are located extrasynaptically, not synaptically [as depicted in figure].) Once inside the neuron, 5-HT can either be repackaged into vesicles for reuse or undergo enzymatic catabolism. The selective serotonin reuptake inhibitors (*SSRIs*) and older-generation tricyclic antidepressants (*TCAs*) are able to interfere with or block the reuptake of 5-HT. 5-HT is metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase (MAO), located on the outer membrane of mitochondria or sequestered and stored in secretory vesicles by vesicular monoamine transporters (VMATs). *Reserpine* causes a depletion of 5-HT in vesicles by interfering with uptake and storage mechanisms (depressive-like symptoms have been reported with this agent). *Tranylcypromine* is an MAO inhibitor (MAOI) and an effective antidepressant. *Fenfluramine* (an anorectic agent) and 3,4-methylenedioxymethamphetamine (*MDMA*; "Ecstasy") are able to facilitate 5-HT release by altering SERT function. cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; IP$_3$ = inositol 1,4,5-triphosphate.

Source. Reprinted from Figure 2-3 (pp. 56-57) in Drazinic CM, Szabo ST, Gould TD, Manji HK: "Neurotransmitters and Receptors in Psychiatric Disorders," in *The American Psychiatric Association Textbook of Psychopharmacology*, 5th Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Association Publishing, 2017, pp. 45-116. Copyright (c) 2017, American Psychiatric Association. Used with permission.

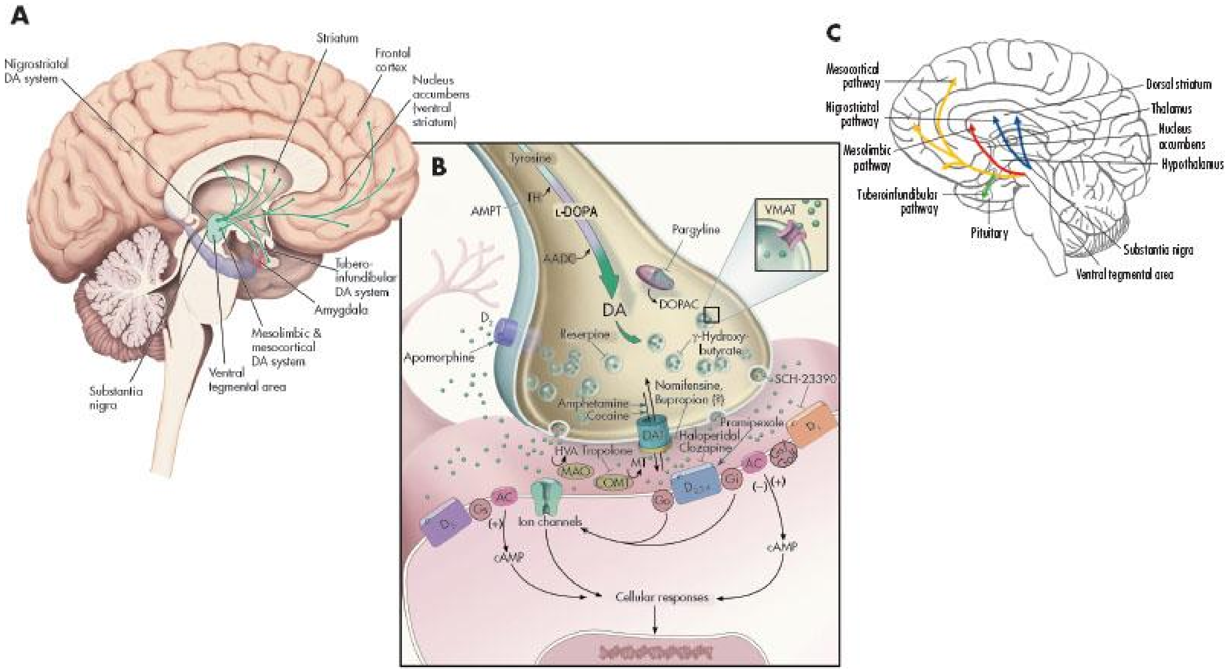

A
Nigrostriatal DA system
Striatum
Frontal cortex
Nucleus accumbens (ventral striatum)
Tubero-infundibular DA system
Amygdala
Mesolimbic & mesocortical DA system
Ventral tegmental area
Substantia nigra
B
Tyrosine
TH
AMPT
L-DOPA
AADC
Pargyline
VMAT
DOPAC
DA
D2
Apomorphine
Reserpine
γ-Hydroxy-butyrate
SCH-23390
Nomifensine, Bupropion (?)
Amphetamine
Cocaine
DAT
Pramipexole
Haloperidol
Clozapine
D1
HVA Tropolone
MAO
COMT
MT
D2,3,4
Gi
AC
Go
Gs
D5
(+)
(–)
Ion channels
cAMP
Cellular responses
C
Mesocortical pathway
Nigrostriatal pathway
Mesolimbic pathway
Tuberoinfundibular pathway
Pituitary
Dorsal striatum
Thalamus
Nucleus accumbens
Hypothalamus
Substantia nigra
Ventral tegmental area

PLATE 11. ***(Figure 2-12)*** **The dopaminergic system.**

(A) Dopaminergic neurons are located in the ventral midbrain in the A9 (substantia nigra pars compacta) and A10 (ventral tegmental area) regions. DA = dopamine.**(B)** Synthesis of dopamine starts with the nonessential amino acid L-tyrosine. The rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase (TH). Aromatic L-amino acid decarboxylase (AADC) then converts L-DOPA to dopamine, which can be metabolized to 3,4-dihydroxyphenylacetic acid (DOPAC) by intraneuronal monoamine oxidase (MAO) or sequestered and stored in secretory vesicles by vesicular monoamine transporters (VMATs). Once released, dopamine acts on pre-and postsynaptic metabotropic receptors and is terminated via reuptake by perisomatic dopamine transporters (DATs). (Note that DATs are located extrasynaptically, not synaptically [as depicted in figure].) AMPT = a-methyl-*p*-tyrosine; cAMP = cyclic adenosine monophosphate; COMT = catechol-O-methyltransferase; HVA = homovanillic acid; MT = methoxytyramine. **(C)** Four separate dopamine pathways are present in the brain that play distinct roles in pathophysiology and therapeutic intervention: the mesocortical pathway (*yellow*), the nigrostriatal pathway (*blue*), the mesolimbic pathway (*red*), and the tuberoinfundibular pathway (*green*).

Source. **Figure parts A and B:** Reprinted from Figure 2-4 (pp. 66-67) in Drazinic CM, Szabo ST, Gould TD, Manji HK: "Neurotransmitters and Receptors in Psychiatric Disorders," in *The American Psychiatric Association Textbook of Psychopharmacology*, 5th Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Association Publishing, 2017, pp. 45-116. Copyright (c) 2017, American Psychiatric Association. Used with permission. **Figure part C:**

Reprinted from Figure 1 (p. 3) of Yang S, Boudier-Reveret M, Choo YJ, Chang MC: "Association Between Chronic Pain and Alterations in the Mesolimbic Dopaminergic System." *Brain Sciences* 10(10):701, 2020 (https://doi.org/10.3390/brainsci10100701). Copyright (c) 2020 by the Authors. Licensee Multidisciplinary Digital Publishing Institute (MDPI), Basel, Switzerland. This article is an Open Access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

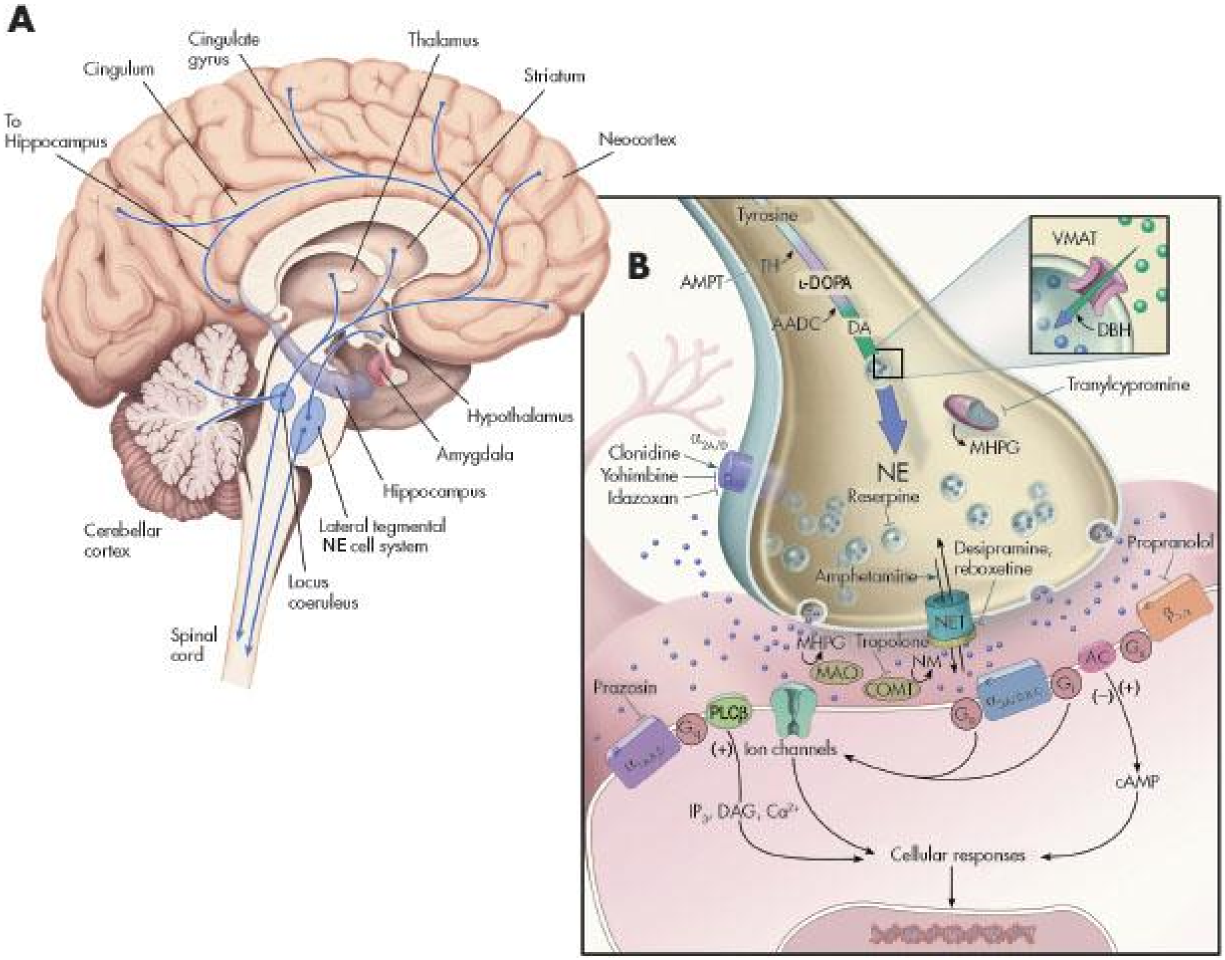

A
Cingulate gyrus
Thalamus
Cingulum
Striatum
To Hippocampus
Neocortex
Hypothalamus
Amygdala
Hippocampus
Cerebellar cortex
Lateral tegmental NE cell system
Locus coeruleus
Spinal cord
B
Tyrosine
AMPT
TH
L-DOPA
AADC
DA
VMAT
DBH
Tranylcypromine
MHPG
Clonidine
Yohimbine
Idazoxan
NE
Reserpine
Desipramine, reboxetine
Amphetamine
Propranolol
NET
MHPG
Tropolone
NM
MAO
COMT
AC
Prazosin
PLCβ
(+) Ion channels
(–) (+)
cAMP
IP₃, DAG, Ca²⁺
Cellular responses

PLATE 12. ***(Figure 2-13)*** **The noradrenergic system**

(A) Noradrenergic neurons of the locus coeruleus are located in the pons of the brain stem. **(B)** Synthesis of norepinephrine (NE) starts with the amino acid L-tyrosine, which is actively transported into presynaptic NE nerve terminals from extracellular fluid. The rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase (TH). Aromatic L-amino acid decarboxylase (AADC) converts L-DOPA to dopamine. Dopamine is then packaged into vesicles, by vesicular monoamine transporters (VMATs), and hydroxylated by dopamine b-hydroxylase (DBH) in the presence of O_2 and ascorbate to form NE. Once released from the presynaptic terminal, NE can interact with a variety of presynaptic and postsynaptic receptors. Presynaptic regulation of NE neuron firing activity and release occurs through somatodendritic (not shown) and nerve terminal a_2 adrenoreceptors, respectively. Binding of NE to G proteins (G_o, G_i, etc.) that are coupled to adenylyl cyclase (AC) and phospholipase C beta (PLCb) produces a cascade of second-messenger and cellular effects. NE's action is terminated when it is taken back into the presynaptic neuron via NE transporters (NETs). (Note that NETs are located extrasynaptically, not synaptically [as depicted in figure].) Once inside the neuron, NE can either be repackaged into vesicles for reuse or undergo enzymatic degradation. AMPT = a-methyl-*p*-tyrosine; cAMP = cyclic adenosine monophosphate; COMT = catechol-O-methyltransferase; DA = dopamine; DAG = diacylglycerol; IP_3 = inositol 1,4,5-triphosphate; MAO = monoamine oxidase; MHPG = 3-methoxy-4-hydroxyphenylglycol; NM = normetanephrine.

Source. Reprinted from Figure 2-5 (pp. 74-75) in Drazinic CM, Szabo ST, Gould TD, Manji HK: "Neurotransmitters and Receptors in Psychiatric Disorders," in *The American Psychiatric Association Textbook of Psychopharmacology*, 5th Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Association Publishing, 2017, pp. 45-116. Copyright (c) 2017, American Psychiatric Association. Used with permission.

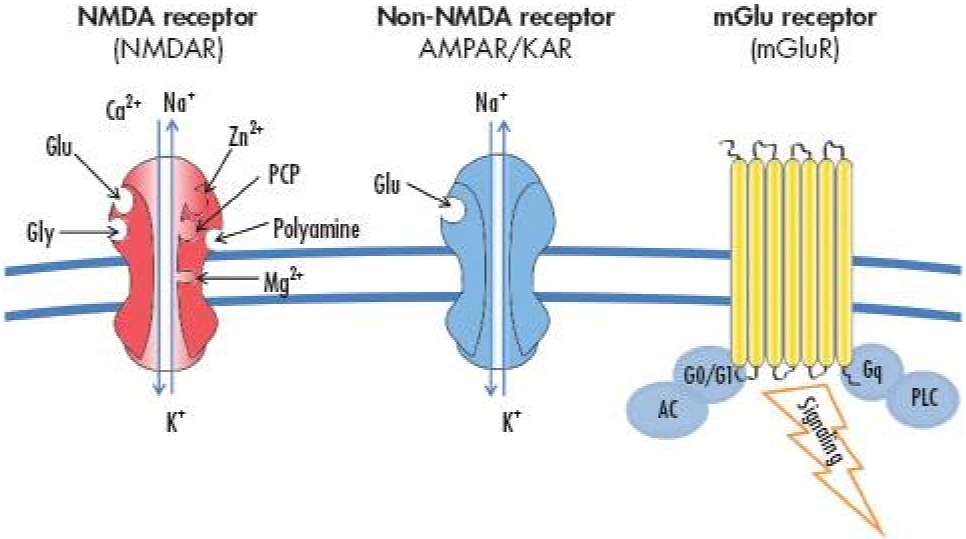


PLATE 13. ***(Figure 2-15)*** **Glutamatergic receptors.**

Ionotropic glutamate receptors mediate fast excitatory signaling in the brain; however, glutamate also plays a modulatory role through activation of metabotropic receptors. The a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors (AMPAR and KAR) are activated by glutamate and are permeable to Na^+, which results in a rapid, transient depolarization of the plasma membrane. In contrast, *N*-methyl-D-aspartate (NMDA) receptors are more complex, being blocked by Mg^{2+} at hyperpolarized membrane potentials and permeable to Ca^{2+}, permitting activation of various intracellular cascades. AC = adenylyl cyclase; G0/G1, Gq = Gi/o protein a subunits; PLC = phospholipase C; PCP = phencyclidine.

Source. Reprinted from Figure 2 (p. 4) in Kritis AA, Stamoula EG, Paniskaki KA, Vavilis TD: "Researching Glutamate-Induced Cytotoxicity in Different Cell Lines: A Comparative/Collective Analysis Study." *Frontiers in Cell Neuroscience* 9, article 91, 2015 (https://doi.org/10.1146/annurev.pharmtox.011008.145533). Copyright (c) 2015, Kritis, Stamoula, Paniskaki, and Vavilis. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CCBY). The use, distribution, or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution, or reproduction is permitted which does not comply with these terms.

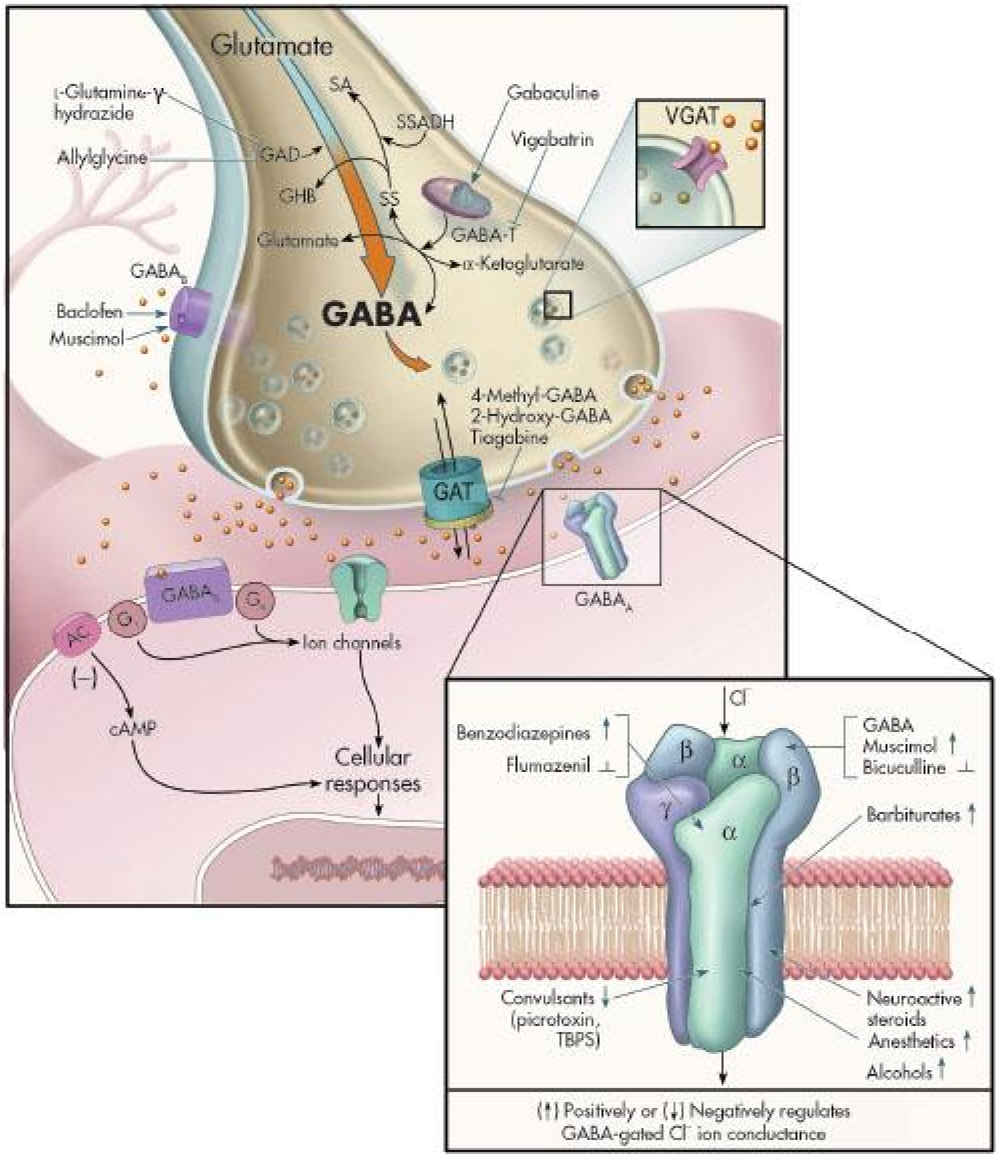

Glutamate
L-Glutamine-γ-hydrazide
Allylglycine
GAD
SA
SSADH
GHB
SS
Glutamate
Gabaculine
Vigabatrin
GABA-T
α-Ketoglutarate
VGAT
GABA
$GABA_B$
Baclofen
Muscimol
4-Methyl-GABA
2-Hydroxy-GABA
Tiagabine
GAT
$GABA_A$
AC
G_i
$GABA_B$
G_o
(–)
Ion channels
cAMP
Cellular responses
Cl^-
Benzodiazepines ↑
Flumazenil ⊥
GABA
Muscimol ↑
Bicuculline ⊥
β
α
β
γ
α
Barbiturates ↑
Convulsants ↓ (picrotoxin, TBPS)
Neuroactive steroids ↑
Anesthetics ↑
Alcohols ↑
(↑) Positively or (↓) Negatively regulates GABA-gated Cl^- ion conductance

PLATE 14. ***(Figure 2-16)*** **The GABAergic system.**

GABA is synthesized from glutamate by the enzyme glutamic acid decarboxylase (GAD) and, following release, binds to both ionotropic GABA_A and metabotropic GABA_B receptors. GABA_A receptors are ligand-gated $\text{Cl}^{[?]}$ channels that hyperpolarize the cell and mediate fast inhibitory signaling in the brain. GABA_A receptors are heteropentameric receptor complexes, composed of numerous subunit isoforms that determine agonist affinity, allosteric modulation, and other channel properties. Note that GABA transporters are located both synaptically (as shown in figure) and extrasynaptically. AC = adenylyl cyclase; cAMP = cyclic adenosine monophosphate; GABA-T = GABA transaminase; GAT = GABA transporter; TBPS = *t*-butylbicyclophosphorothionate; VGAT = vesicular GABA transporter.

Source. Reprinted from Figure 2-8 (pp. 94-95) in Drazinic CM, Szabo ST, Gould TD, Manji HK: "Neurotransmitters and Receptors in Psychiatric Disorders," in *The American Psychiatric Association Textbook of Psychopharmacology*, 5th Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Association Publishing, 2017, pp. 45-116. Copyright (c) 2017, American Psychiatric Association. Used with permission.

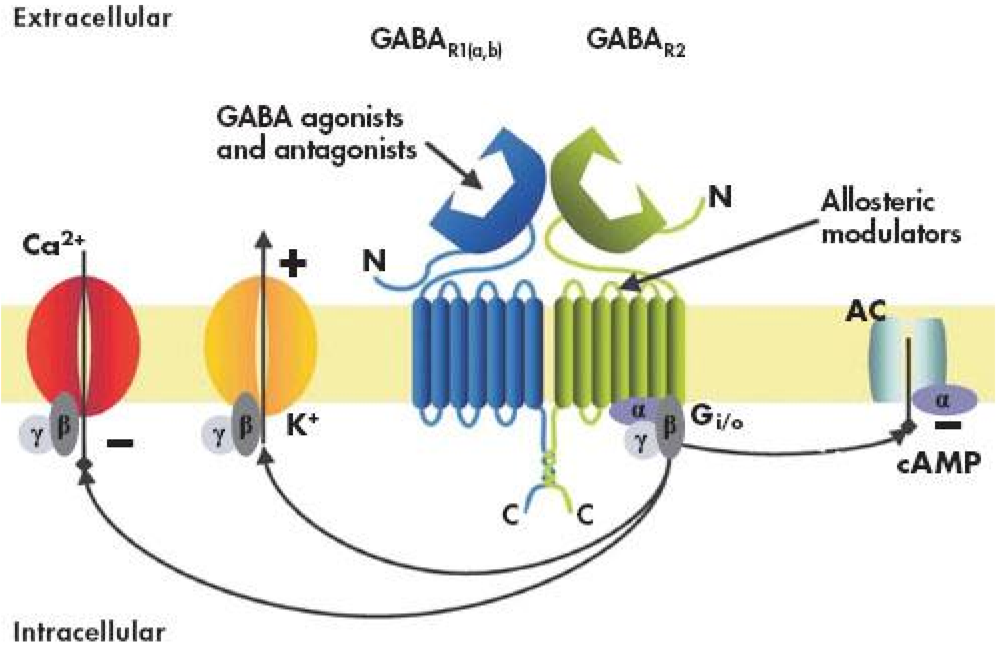
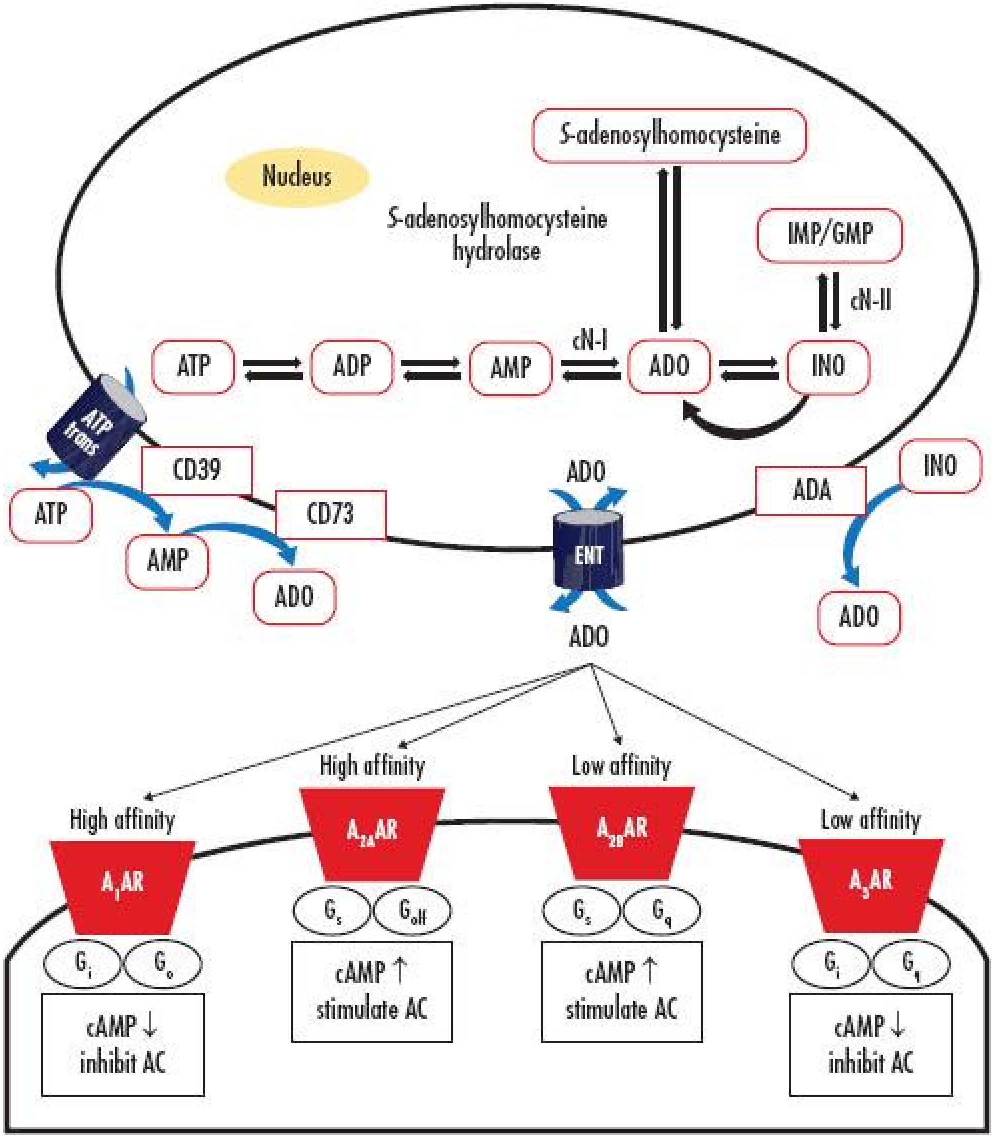


PLATE 15. ***(Figure 2-17)*** **$GABA_B$ receptors.**

The metabotropic $GABA_B$ receptors are GPCRs assembled as heterodimers from two subunits of the receptor ($GABA_{B1}$ and $GABA_{B2}$) coupled to $G_{i/o}$. Activation of $GABA_B$ receptors inhibits adenylyl cyclase, decreasing cAMP production. In addition, the Gbg subunit directly activates G protein-activated K^+ channels and inhibits voltage-gated Ca^{2+} channels, resulting in neuronal inhibition. AC = adenylyl cyclase; C = C-terminus; cAMP = cyclic adenosine monophosphate; $GABA_{R1(a,b)}$, $GABA_{R2}$ = $GABA_{B1}$ subunits; $G_{i/o}$ = Gi/o protein a subunit; N = N-terminus.

Source. Reprinted from Figure 1 (p. 756) in Filip M, Frankowska M: "Effects of GABA(B) Receptor Agents on Cocaine Priming, Discrete Contextual Cue and Food Induced Relapses." *European Journal of Pharmacology* 571(2-3):166-173, 2007 (https://doi.org/10.1016/j.ejphar.2007.05.069). Copyright (c) 2007, Elsevier B.V. Used with permission.



Nucleus
S-adenosylhomocysteine
S-adenosylhomocysteine hydrolase
IMP/GMP
cN-II
ATP
ADP
AMP
cN-I
ADO
INO
ATP trans
CD39
CD73
ATP
AMP
ADO
ADO
ENT
ADO
ADA
INO
ADO
High affinity
High affinity
Low affinity
Low affinity
A1AR
A2AAR
A2BAR
A3AR
Gi
Go
Gs
Golf
Gs
Gq
Gi
Gq
cAMP ↓ inhibit AC
cAMP ↑ stimulate AC
cAMP ↑ stimulate AC
cAMP ↓ inhibit AC

PLATE 16. ***(Figure 2-18)*** **Production, transport, and metabolism of adenosine.**

Intracellular adenosine is produced via dephosphorylation from the main source, AMP, via both cN-I and cN-II and hydrolysis of *S*-adenosyl-homocysteine through the enzyme *S*-adenosyl-L-homocysteine hydrolase. The extracellular formation of adenosine is the result of enzymatic cascades consisting of ATP transport, hydrolysis of ATP and ADP by CD39 to form AMP, and dephosphorylation of AMP by CD73. Extracellular adenosine binds adenosine receptors (A_1AR, A_{2A}AR, A_{2B}AR, and A_3AR) on the surface of cells. Each adenosine receptor is a GPCR that transmits the signal from adenosine by stimulating or inhibiting cyclic AMP (cAMP). AC = adenylyl cyclase; ADA = adenosine deaminase; ADO = adenosine; ADP = 5'-adenosine diphosphate; AMP = 5'-adenosine monophosphate; AR = adenosine receptor; ATP = 5'-adenosine triphosphate; CD = ectonucleotidase cluster of differentiation; cN = cytosolic 5'-nucleotidase; ENT = equilibrative nucleoside transporter; GMP = guanosine monophosphate; GPCR = G protein-coupled receptor; IMP = inosine monophosphate; INO = inosine.

Source. Reprinted from Figure 1 (p. 3) in Effendi WI, Nagano T, Kobayashi K, et al.: "Focusing on Adenosine Receptors as a Potential Targeted Therapy in Human Diseases." *Cells* 9(3):785, 2020 (https://doi.org/10.3390/cells9030785). Copyright (c) 2020 by the Authors. Licensee Multidisciplinary Digital Publishing Institute (MDPI), Basel, Switzerland. This article is an Open Access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

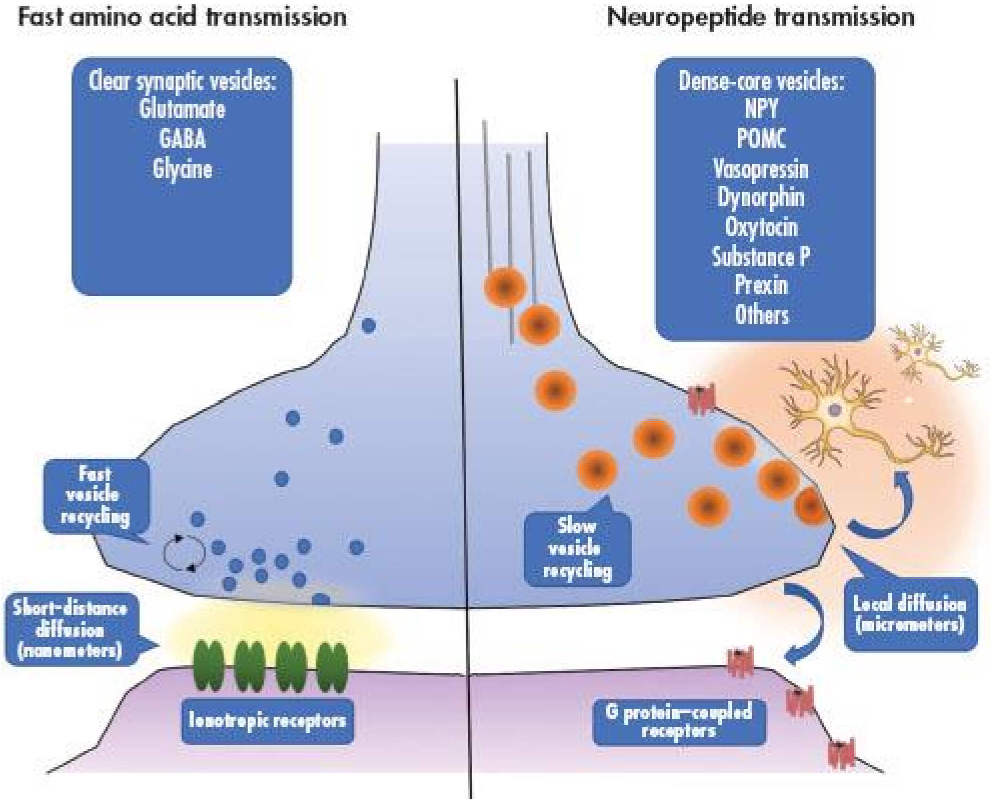

Fast amino acid transmission
Neuropeptide transmission
Clear synaptic vesicles: Glutamate GABA Glycine
Dense-core vesicles: NPY POMC Vasopressin Dynorphin Oxytocin Substance P Prexin Others
Fast vesicle recycling
Slow vesicle recycling
Short-distance diffusion (nanometers)
Local diffusion (micrometers)
Ionotropic receptors
G protein–coupled receptors

PLATE 17. *(Figure 2-19)* Comparison of fast amino acid synaptic transmission *(left)* and slower neuropeptide transmission *(right)*.

NPY = neuropeptide Y; POMC = pro-opiomelanocortin.

Source. Adapted from Figure 3 (p. 103) in van den Pol AN: "Neuropeptide Transmission in Brain Circuits." *Neuron* 76(1):98-115, 2012 (https://doi.org/10.1016/j.neuron.2012.09.014). Copyright (c) 2012, Elsevier, Inc. Used with permission.

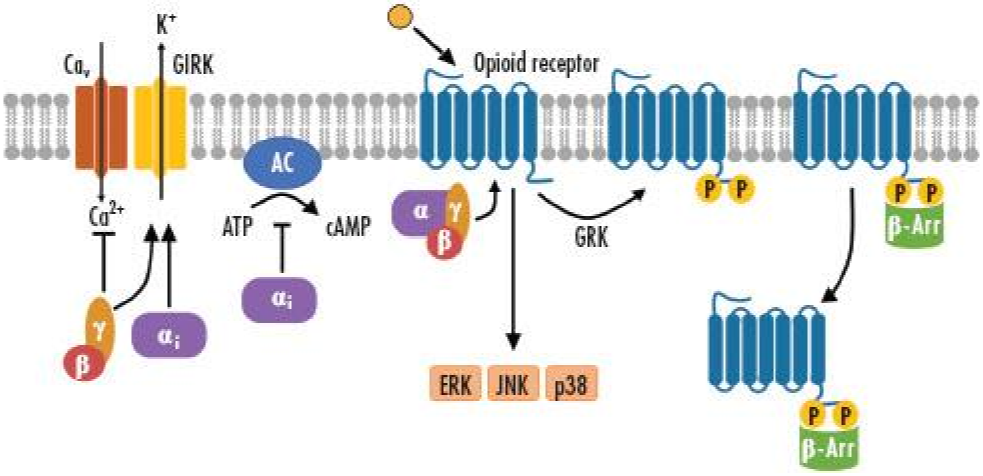

K+
Ca_v
GIRK
Opioid receptor
AC
Ca2+
ATP
cAMP
α
γ
β
αi
γ
β
αi
GRK
P
P
P
P
β-Arr
ERK
JNK
p38
P
P
β-Arr

PLATE 18. ***(Figure 2-20)*** **Opioid receptor-mediated signaling.**

AC = adenylyl cyclase; a_i = G protein a i subunit; b-Arr = b-arrestins; ATP = 5'-adenosine triphosphate; Ca^{2+} = calcium ions; cAMP = cyclic adenosine monophosphate; Ca_v = voltage-gated calcium ion channel; ERK = extracellular signal-regulated kinase; GIRK = G protein-coupled inwardly rectifying potassium [channel]; GRK = G protein receptor kinase; K^+ = potassium ions; JNK = c-Jun N-terminal kinase; P = phosphorus; p38 = p38 mitogen-activated protein kinase (MAPK). a and bg refer to the respective heterotrimeric G protein subunits. See section "G Protein-Coupled Receptors" for details.

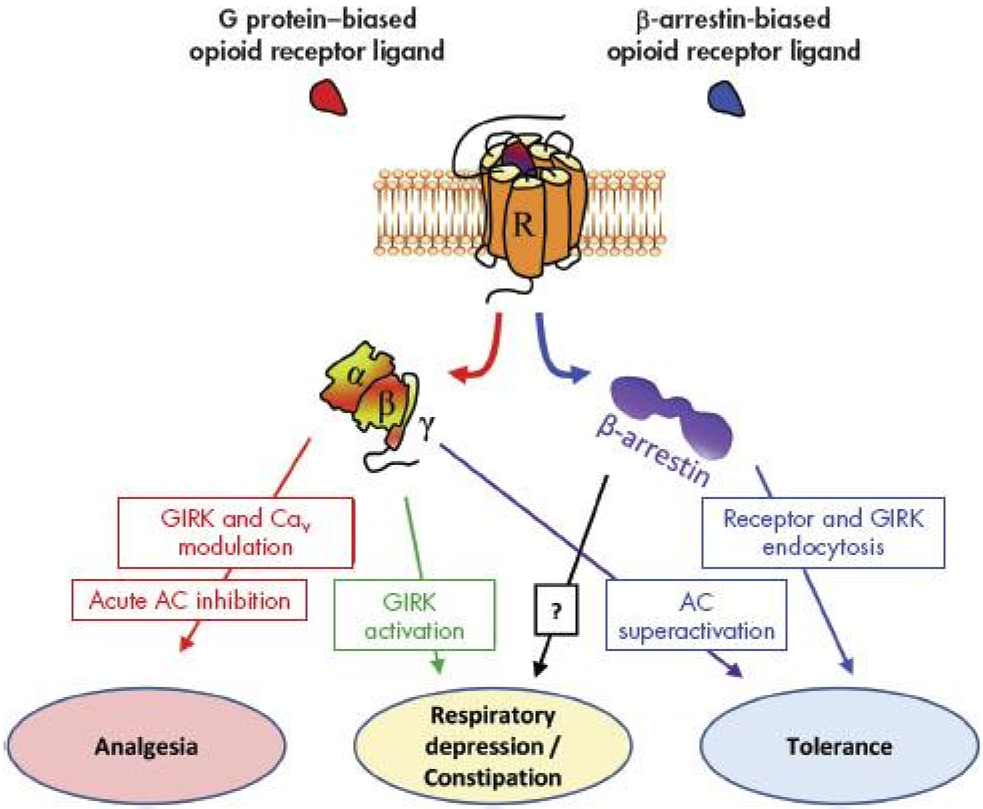

G protein–biased opioid receptor ligand
β-arrestin-biased opioid receptor ligand
R
α
β
γ
β-arrestin
GIRK and Ca_V modulation
Acute AC inhibition
GIRK activation
?
AC superactivation
Receptor and GIRK endocytosis
Analgesia
Respiratory depression / Constipation
Tolerance

PLATE 19. *(Figure 2-21)* Signaling bias of opioid ligands.

Opioid receptor activation of G protein signaling leading to increased ion channel activity (GIRK and Ca_V channels) and inhibition of AC was thought to mediate analgesia, whereas b-arrestin signaling was associated with adverse side effects (e.g., constipation, respiratory depression). However, more recent studies suggest that b-arrestin signaling may not underlie the development of constipation and respiratory depression, whereas G protein-mediated pathways may contribute to the development of these adverse effects. AC = adenylyl cyclase; Ca_V = voltage-gated calcium channel; GIRK = G protein-coupled inwardly rectifying potassium [channel].

Source. Reprinted from Figure 1 (p. 2) in Pineyro G, Nagi K: "Signaling Diversity of Mu-and Delta-Opioid Receptor Ligands: Re-Evaluating the Benefits of b-Arrestin/G Protein Signaling Bias." *Cellular Signalling* 80:109906, 2021 (https://doi.org/10.1016/j.cellsig.2020.109906). Licensed under a Creative Commons Attribution 4.0 license; https://creativecommons.org/licenses/by/4.0.

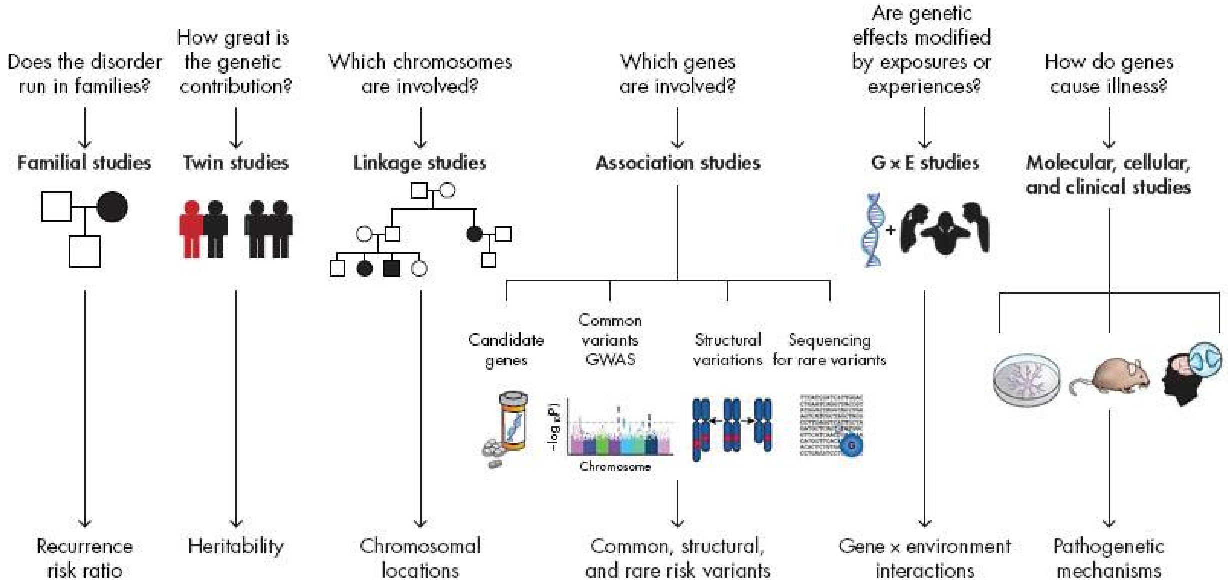

Does the disorder run in families?
How great is the genetic contribution?
Which chromosomes are involved?
Which genes are involved?
Are genetic effects modified by exposures or experiences?
How do genes cause illness?
Familial studies
Twin studies
Linkage studies
Association studies
G × E studies
Molecular, cellular, and clinical studies
Candidate genes
Common variants GWAS
Structural variations
Sequencing for rare variants
–log10(P)
Chromosome
Recurrence risk ratio
Heritability
Chromosomal locations
Common, structural, and rare risk variants
Gene × environment interactions
Pathogenetic mechanisms

PLATE 20. ***(Figure 3-1)*** **Overview of genetic methods used in psychiatry research.**

This figure summarizes the different steps from heritability to understanding pathomechanisms using genetic methods. G x E = gene x environment; GWAS = genome-wide association studies.

Source. Adapted from Figure 1 (p. 298) in Smoller JW: "The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders." *Neuropsychopharmacology* 41(1):297-319, 2016 (https://doi.org/10.1038/npp.2015.266). Copyright (c) 2016, American College of Neuropsychopharmacology.

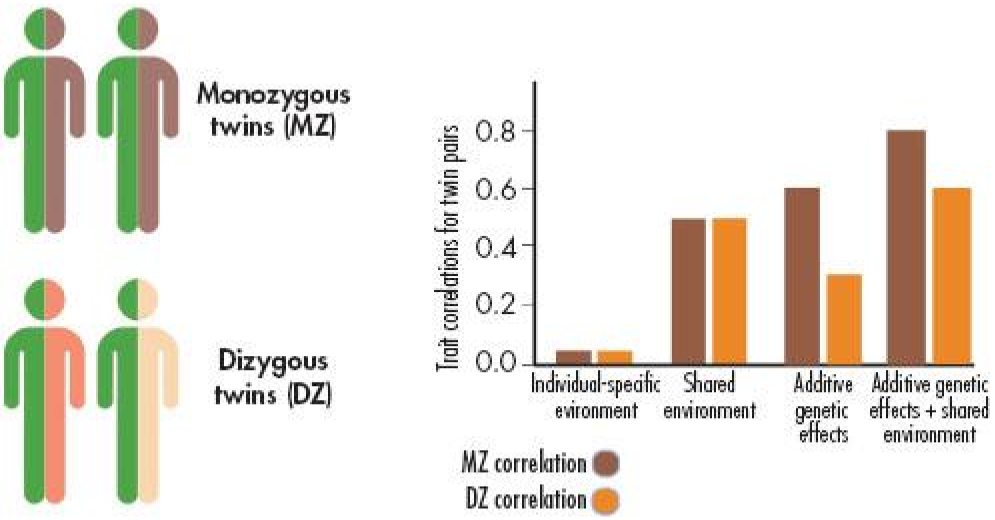


PLATE 21. ***(Figure 3-2)*** **Patterns of intrapair correlations in twins and the source of variance implied.**

Correlation of phenotypes/traits between monozygotic (MZ) and dizygotic (DZ) twin pairs illustrating different scenarios of genetic and environmental contributions to disease. Intrapair correlations of around zero imply effects of individual-specific environment. Equal intrapair correlations that are greater than zero for MZ and DZ twins imply effects of shared environment. Correlations for MZ twins that are twice as great as those for DZ twins imply additive genetic effects. Correlations for MZ twins that are greater than--but not twice as great as--those for DZ twins imply additive genetic effects and shared environment effects. Correlations of less than 1.0 are likely mediated by individual-specific environment effects.

Source. Created with BioRender.com.

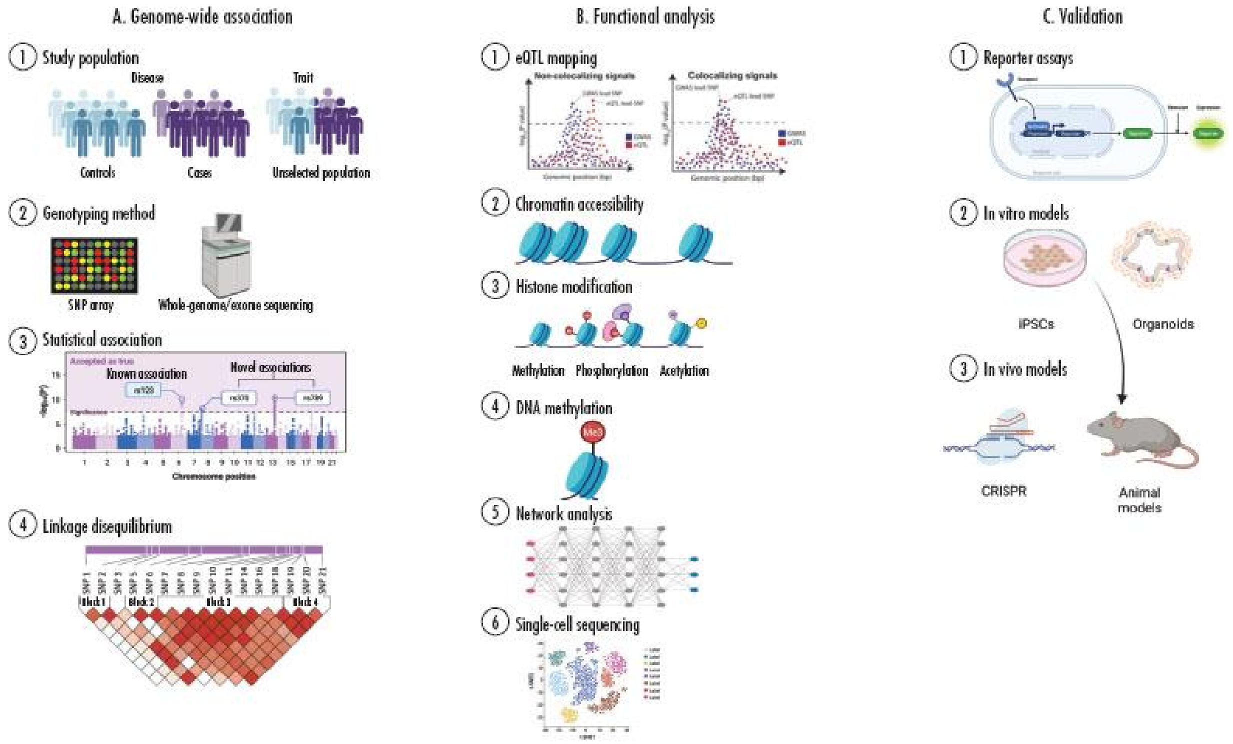

A. Genome-wide association
1 Study population
Disease
Trait
Controls
Cases
Unselected population
2 Genotyping method
SNP array
Whole-genome/exome sequencing
3 Statistical association
Known association
Novel associations
Chromosome position
4 Linkage disequilibrium
Block 1
Block 2
Block 3
Block 4
B. Functional analysis
1 eQTL mapping
Non-colocalizing signals
Colocalizing signals
2 Chromatin accessibility
3 Histone modification
Methylation
Phosphorylation
Acetylation
4 DNA methylation
Me3
5 Network analysis
6 Single-cell sequencing
C. Validation
1 Reporter assays
2 In vitro models
iPSCs
Organoids
3 In vivo models
CRISPR
Animal models

PLATE 22. ***(Figure 3-3)*** **From association to function** ***(next page)*.**

(A) Genome-wide association studies (GWAS) are used to detect associations between a specific phenotype and the frequency of single nucleotide polymorphisms (SNPs). ***(1) Study population*** selection. Cases and controls can be compared for disease associations, or a population can be used to measures associations with quantitative traits. ***(2) Genotyping methods*** include SNP arrays and whole-genome/exome sequencing. ***(3) Statistical tests*** (in this case a Manhattan plot) can be used to detect associations between regions of the genome and the trait of interest. ***(4)*** Genotyped SNPs are in ***linkage disequilibrium*** (LD) with causal variants. This panel shows an LD matrix plot, where the color intensity is proportionate to linkage strength. **(B) Functional analysis of genetic variants.** Epigenetic investigations include the following: ***(1) Expression quantitative trait locus (eQTL) analysis***. Patterns of associations of GWAS and eQTLs can tell us whether they are both being driven by the same causal variant in LD. ***(2-4)*** Different marks to measure the functionality of regulatory elements: ***(2) chromatin accessibility***, ***(3) histone modification***, and ***(4) DNA methylation***. Me3 = methylation mark. ***(5)*** Gene expression ***network analysis*** allows one to interpret functionality based on gene network correlations. ***(6) Single-cell sequencing*** now allows one to map gene expression profile and QTLs to specific cell types. t-SNE = t-distributed stochastic neighbor embedding. **(C) Validation of findings.** ***(1)*** Genetic variants of interest can be validated using ***reporter assays*** to confirm their regulatory effects. ***(2) In vitro models.*** Induced pluripotent stem cells (iPSCs) and derived cells and organoids allow one to investigate genetic variants in the human context. ***(3)***

Humanized ***animal models*** (using CRISPR [clustered regularly interspaced short palindromic repeats] technologies or by human iPSC-derived cell transplantation) allow one to explore circuit-level and behavioral consequences of specific genetic variants or of cells carrying these variants.
Source. Created with BioRender.com.

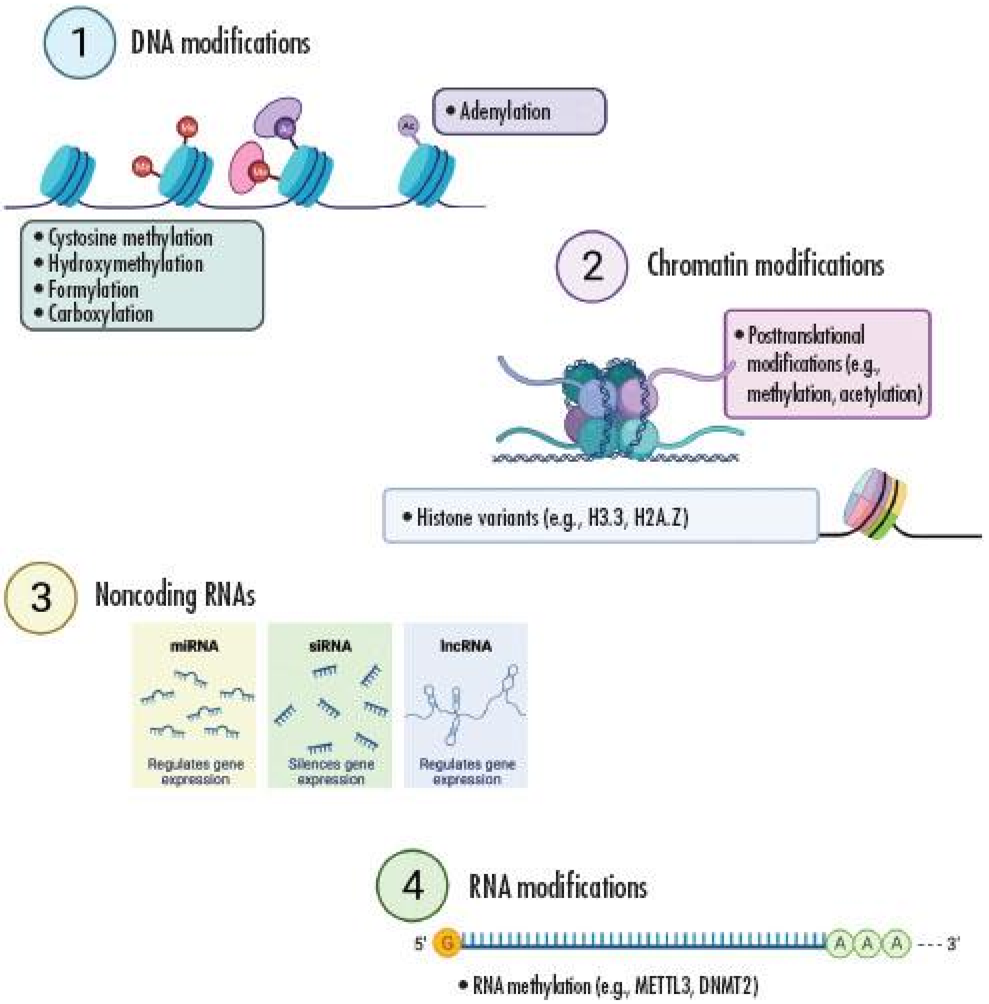

1 DNA modifications
• Adenylation
• Cystosine methylation
• Hydroxymethylation
• Formylation
• Carboxylation
2 Chromatin modifications
• Posttranslational modifications (e.g., methylation, acetylation)
• Histone variants (e.g., H3.3, H2A.Z)
3 Noncoding RNAs
miRNA
Regulates gene expression
siRNA
Silences gene expression
lncRNA
Regulates gene expression
4 RNA modifications
5'
G
A
A
A
3'
• RNA methylation (e.g., METTL3, DNMT2)

PLATE 23. ***(Figure 3-5)*** **Epigenetic mechanisms.**

This figure summarizes the different types of epigenetic modifications. **(1)** DNA modifications: Cytosines can be modified by methylation, hydroxymethylation, formylation, and carboxylation, whereas adenines can only be modified by methylation (adenylation). **(2)** Chromatin modifications: Nucleosomes, composed of DNA wrapped around histone proteins, can change position to increase or decrease DNA accessibility. Nucleosomes also can be modified by adding histone variants and posttranslational modifications. **(3)** Noncoding RNAs can regulate transcription and thus are also considered an epigenetic mechanism. **(4)** RNA modifications (epitranscriptomics): Gene expression can be influenced by RNA modifications, which are also reversible. DNMT2 = DNA methyltransferase-like protein 2; METTL3 = methyltransferase-like 3.

Source. Created with BioRender.com.

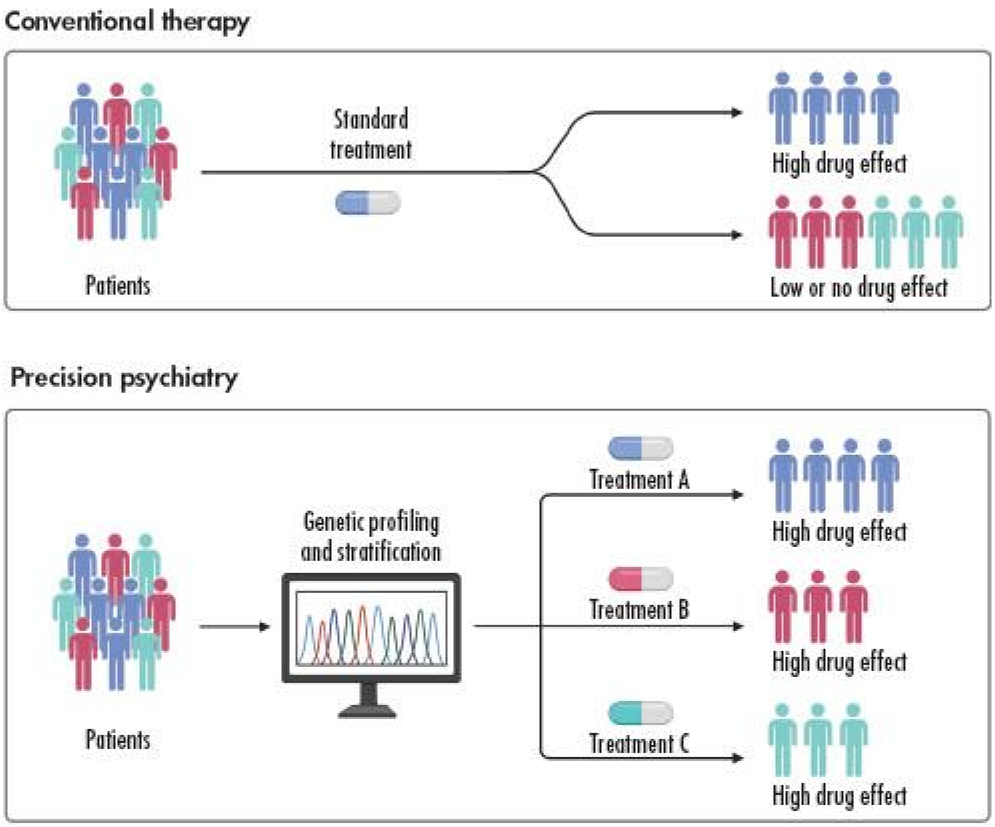

Conventional therapy
Patients
Standard treatment
High drug effect
Low or no drug effect
Precision psychiatry
Patients
Genetic profiling and stratification
Treatment A
High drug effect
Treatment B
High drug effect
Treatment C
High drug effect

PLATE 24. ***(Figure 3-6)*** **Precision psychiatry.**

Genetic profiling together with other measures may allow patient stratification that can be used to target treatments more efficiently.

Source. Created with BioRender.com.

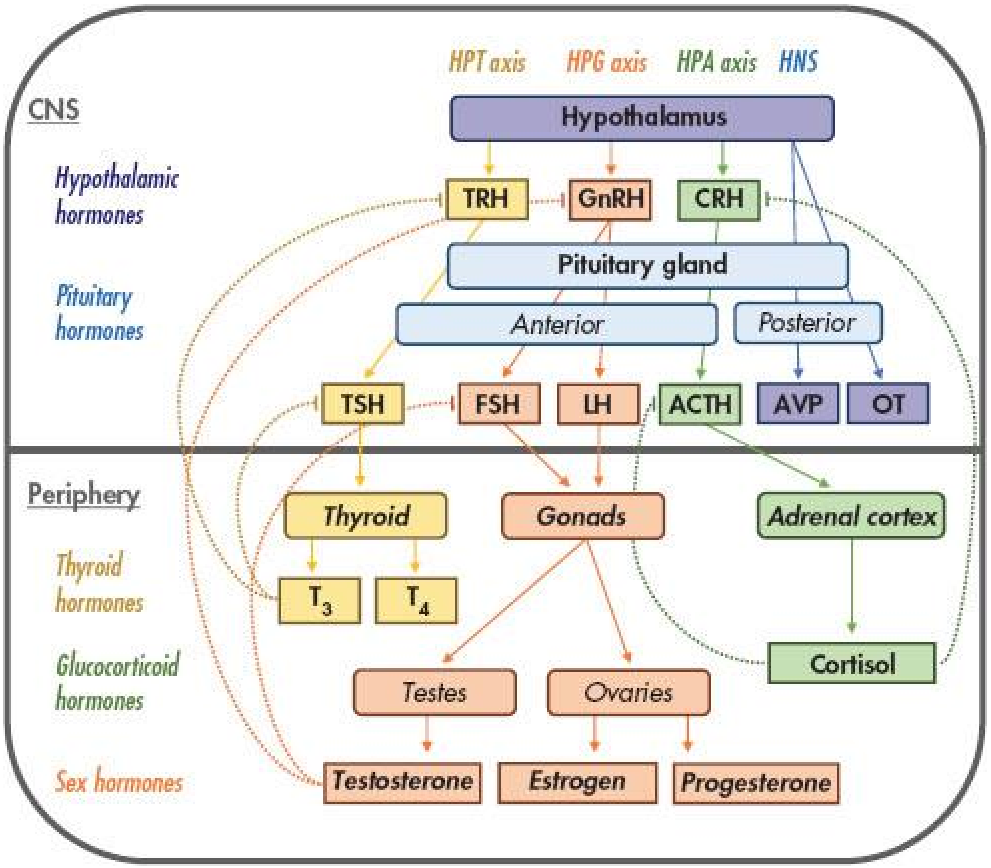

HPT axis
HPG axis
HPA axis
HNS
CNS
Hypothalamus
Hypothalamic hormones
TRH
GnRH
CRH
Pituitary gland
Pituitary hormones
Anterior
Posterior
TSH
FSH
LH
ACTH
AVP
OT
Periphery
Thyroid
Gonads
Adrenal cortex
Thyroid hormones
T_3
T_4
Glucocorticoid hormones
Cortisol
Testes
Ovaries
Sex hormones
Testosterone
Estrogen
Progesterone

PLATE 25. ***(Figure 4-1)*** **Physiology of the neuroendocrine system.**

Schematic representation of the four major neuroendrocrine elements: the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), and hypothalamic-pituitary-gonadal (HPG) axes and the hypothalamic-neurohypophyseal system (HNS). Hypothalamic neurons produce releasing hormones and HNS hormones. Releasing hormones act on the anterior pituitary gland, causing the release of stimulating hormones. HNS hormones are released from hypothalamic axons in the posterior pituitary, or neurohypophysis. The stimulating hormones produced in the pituitary gland stimulate peripheral organs (thyroid, gonads, and adrenal cortex) to produce specific hormones, which in turn exert several biological functions (T_3, T_4; testosterone, progesterone, estrogens; and cortisol, respectively). These peripheral hormones can act backwards within each axis, self-controlling their production in a negative feedback loop. The HPT axis is represented in *yellow*; the HPG in *red*; the HPA in *green*; the hypothalamus and HNS in *blue*; and the pituitary gland in *light blue*. *Arrows* indicate stimulation, and *dotted lines* indicate inhibition. Hormone-producing organs are described in *rounded boxes*, and hormonal products are depicted as *rectangles*. ACTH = adrenocorticotropic hormone; AVP = arginine vasopressin; CNS = central nervous system; CRH = corticotropin-releasing hormone; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; OT = oxytocin; T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

Source. Reprinted from Figure 6-1 (p. 107) in Sforzini L, Nettis MA, Weston FI, Pariante CM: "Psychoneuroendocrinology of Mood Disorders," in The American Psychiatric Association Textbook of Mood Disorders, 2nd Edition. Edited by Nemeroff CB, Rasgon N, Schatzberg AF, Strakowski SM. Washington, DC, American Psychiatric Association Publishing, 2022, pp. 105-131. Copyright (c) 2022, American Psychiatric Association. Used with permission.

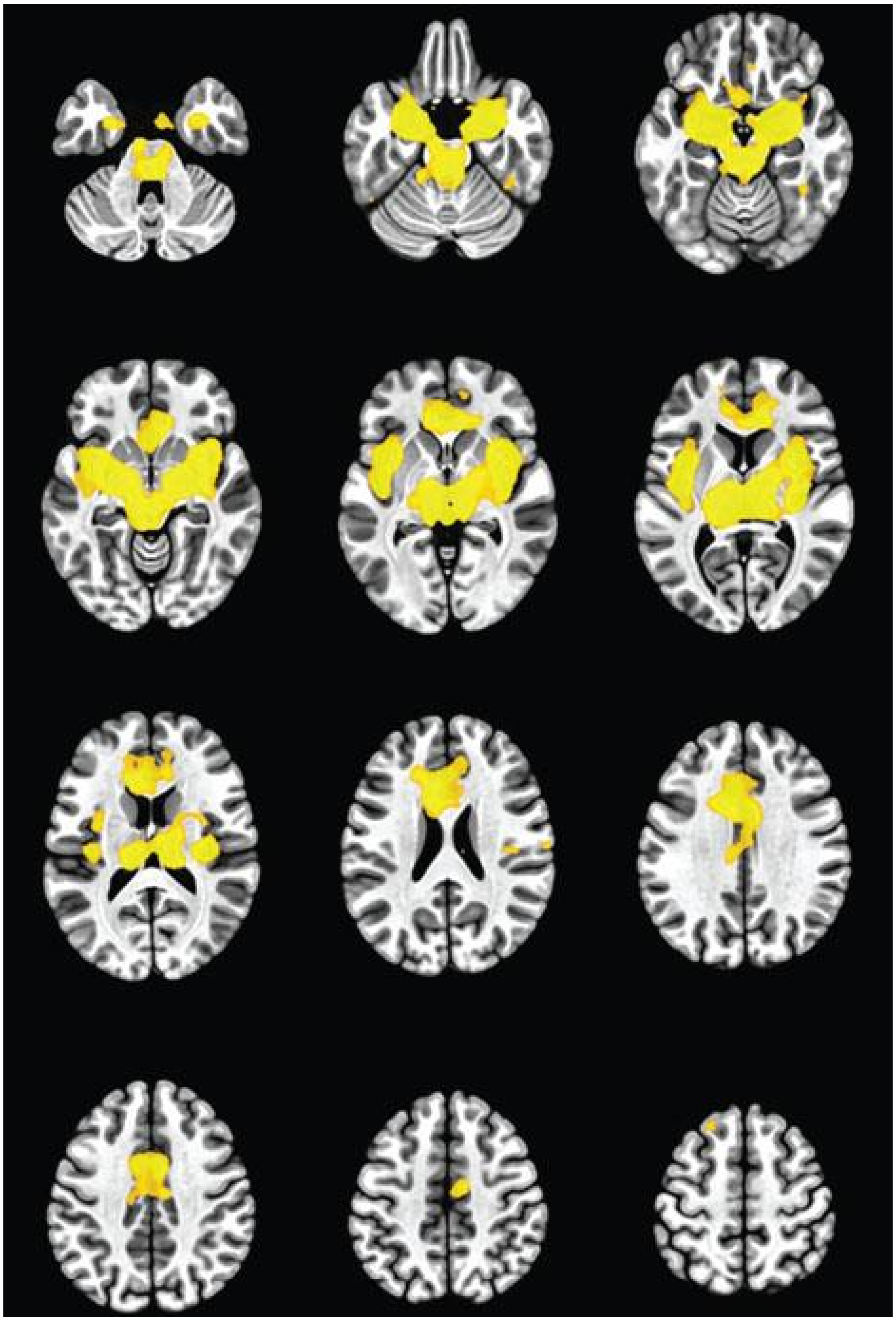


PLATE 26. ***(Figure 7-1)*** **Axial slices of prospective meta-analysis using NeuroQuery,[a] indicating the predicted activations to the keywords "anticipation, emotion, anxiety, depression."**

The color codes represent thresholded (at 3.0) z values. As indicated in the text, the following brain structures are predicted to be significantly activated: midline cortical structures, insula, amygdala, and thalamus.

[a] NeuroQuery (neuroquery.org; Dockes *et al.* 2020).

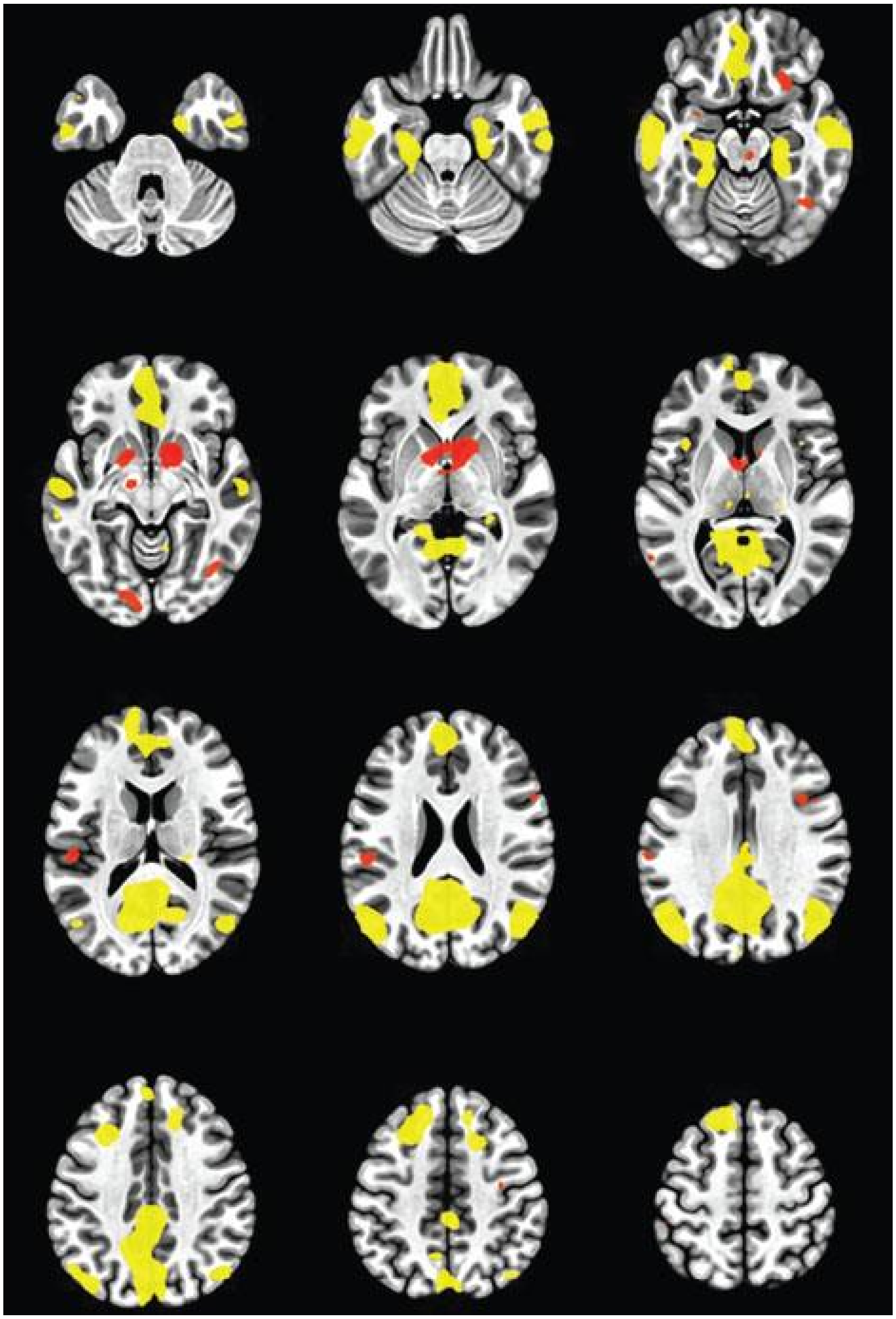


PLATE 27. ***(Figure 7-2)*** **Axial slices of prospective meta-analysis using NeuroQuery,[a] indicating the predicted activations to the keywords "formal thought disorder, schizophrenia."**

The color codes represent thresholded (at 3.0) z values. As indicated in the text, the following brain structures are predicted to be significantly activated: posterior cingulate, midline cortical structures, precuneus, superior temporal gyrus, and middle frontal gyrus.

[a] NeuroQuery (neuroquery.org; Dockes *et al.* 2020).

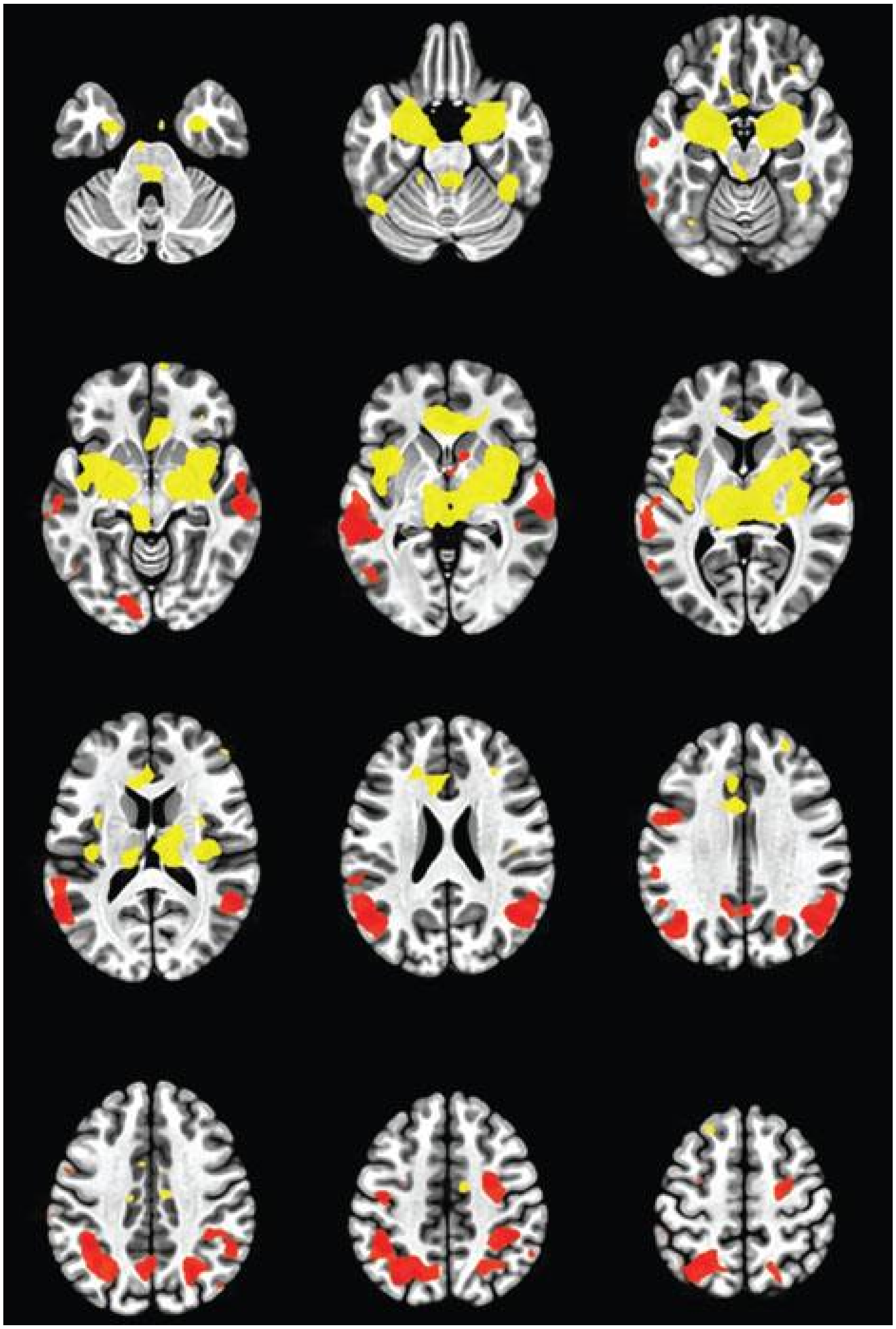


PLATE 28. ***(Figure 7-3)*** **Axial slices of prospective meta-analysis using NeuroQuery,[a] indicating the predicted activations to the keywords "antidepressant, treatment, emotion."**

The color codes represent thresholded (at 3.0) z values. As indicated in the text, the following brain structures are predicted to be significantly activated: amygdala, insula, anterior cingulate, posterior parietal, and thalamus.

[a] NeuroQuery (neuroquery.org; Dockes *et al.* 2020).

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EDITED BY

Alan F. Schatzberg, M.D.

Charles B. Nemeroff, M.D., Ph.D

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Note: The authors have worked to ensure that all information in this book is accurate at the time of publication and consistent with general psychiatric and medical standards, and that information concerning drug dosages, schedules, and routes of administration is accurate at the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice continue to advance, however, therapeutic standards may change. Moreover, specific situations may require a specific therapeutic response not included in this book. For these reasons and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of physicians directly involved in their care or the care of a member of their family.

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This Textbook is dedicated to our grandchildren-- Charlie, Brooks, Emilia, Lily, and Charlotte (AFS) and Emily, Callie, Elise, Bridget, and Logan (CBN) --who give us so much joy every day.

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Introduction

In 1996, we published the first edition of the *Textbook of Psychopharmacology*, which was generally acknowledged as an immediate success, and we are delighted that the sixth edition of *The American Psychiatric Association Publishing Textbook of Psychopharmacology* is now being published. The field has grown greatly in the past 25-plus years, with amazing advances in neuroscience, psychopharmacology, and brain stimulation therapies. Commensurate with this growth, we have with each edition tried to present the most salient information both from basic neuroscience as it relates to the pathogenesis and pathophysiology underlying psychiatric disorders and from basic and clinical psychopharmacology. Each successive edition has understandably become larger as we have attempted to keep pace with the ever-growing body of knowledge in the field. The *Textbook* now has more than 160 authors--including more than 75 new contributors. It has 12 all-new chapters, and it is fully aligned with the revised DSM-5-TR classification. This Sixth Edition is published in two volumes.

The opening section in Volume 1--Principles of Neuropsychopharmacology--contains 9 chapters and provides a tour of the multiple disciplines that undergird the chapters to come, with topics extending from the principles of molecular biology and genomics to the rudiments of neuroimaging and personalized medicine in psychiatry. The second section--Classes of Psychiatric Treatments--contains 38 chapters and provides a comprehensive examination of the medication classes used in psychopharmacological treatment as well as the available neuromodulation therapies. For each drug within a class, data are reviewed on history and discovery, preclinical and clinical pharmacology, pharmacokinetic parameters, mechanism of action, indications and efficacy, side effects and toxicology, and drug-drug interactions. Similar data are provided for brain stimulation modalities. A detailed Index closes this volume.

Volume 2 of the *Textbook* contains the third and final section--Psychopharmacological Treatment--and consists of 20 chapters focused on psychopharmacological approaches to treatment of patients with major psychiatric disorders (e.g., mood and anxiety disorders, schizophrenia, substance use disorders) as well as patients in specific populations (e.g., adults with ADHD, pediatric patients). For each specific condition, patient population, or setting, chapters provide guidance on topics such as medication selection, combination and maintenance dosing regimens, side-effect monitoring and management, and optimization of treatment response. Following these chapters is an Appendix of Psychiatric Medications, with key information on each of the agents covered in the *Textbook*, presented in a convenient tabular format. A detailed Index closes this volume.

Noteworthy additions to this *Textbook* include chapters addressing the following topics:

- Potential roles of personalized medicine in psychiatry and of artificial intelligence and machine learning in psychopharmacology
- New medications with novel pharmacological mechanisms, including ketamine and esketamine, the neurosteroid antidepressant brexanolone, and the atypical antipsychotic pimavanserin
- Use of investigational agents, such as psychedelics, in psychiatric treatment
- Treatment of alcohol use disorder, PTSD, OCD, and autism spectrum disorder
- Treatment of ADHD in adults
- Treatment of women in all life phases, including during pregnancy and the postpartum period
- Treatment of individuals with intellectual developmental disorder

With a level of detail not found in any other source, our new edition of *The American Psychiatric Association Publishing Textbook of Psychopharmacology* illuminates the path to effective evidence-based practice of psychopharmacology for novice and seasoned clinicians alike. We hope you will share our great enthusiasm for this Sixth Edition of the *Textbook of Psychopharmacology*.

This *Textbook* would not have been possible without the superb work of our managing editors, Adrienne Bronfeld and Kelly Puzdrak, who coordinated the efforts and time lines of the chapter authors. In addition, we wish to thank John McDuffie, who recently retired from his position as Publisher of American Psychiatric Association Publishing, for his support of this and previous editions. Greg Kuny, Managing Editor for Books, who also retired recently, has been steadfast in his editing and handling of the details of manuscript preparation. We are fortunate that his successor, Jennifer Gilbreath, has taken on this role for the Sixth Edition *Textbook*. We also are appreciative of the efforts of Rebecca Richters (Senior Editor, Books), Tammy Cordova (Senior Graphic Design Manager), Judy Castagna (Assistant Director of Production Services), and Erika Parker (Acquisitions Editor), Annie Birge (Acquisitions Coordinator), Christie Couture (Associate Director, Marketing), and Margaret May (Marketing Associate) on this and other textbooks we have edited. Robert B. MacArthur, Pharm.D., has provided superb editorial assistance in ensuring accurate information regarding formulations and dosages of all available medications. Finally, Saul Levin, Medical Director of the American Psychiatric Association, and Laura Roberts, Editor-in-Chief, have our eternal gratitude for their support on this project.

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PART III

Psychopharmacological Treatment

CHAPTER 48

Treatment of Depression

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Major depressive disorder (MDD) is a common and debilitating illness that affects people across the world. DSM-5 defines MDD as the co-occurrence of five or more defined symptoms for 2 weeks or more, including "depressed mood" or "loss of interest or pleasure," that confer substantial impairment in functioning indicative of a distinct change from a person's nondepressed functional status (American Psychiatric Association 2013). Disruptions in sleep (insomnia or hypersomnia), appetite (anorexia or hyperphagia), energy level (fatigue), and cognition (impaired concentration, indecisiveness) are common. Negative cognitions including feelings of worthlessness or guilt are also common and sometimes associated with suicidal ideation and behavior, a worrisome complication.

For 2021, the National Institute of Mental Health (NIMH) reported an annual MDD prevalence of 8.3% for adults in the United States, with women being more often affected (10.3%) than men (6.2%). The 18-to 25-year-old age group appears to be particularly vulnerable, with the highest MDD subgroup prevalence of 18.6%. Among U.S. adults experiencing a major depressive episode (MDE) with severe impairment, an estimated 74.8% received treatment (National Institute of Mental Health 2023). In line with reported prevalence values, the economic burden of MDD is astounding, with annual U.S. estimates exceeding $200 billion and a calculated annual incremental health care cost of $6,400 beyond the cost for people without MDD (Greenberg *et al.* 2015).

The goal of treatment in MDD is to achieve full remission, defined as minimal or complete absence of depressive symptoms, with full restoration of psychosocial function. This goal is driven largely by epidemiological observations, namely that residual depressive symptoms are a risk factor for relapse and recurrence of MDD, and chronicity of depressive symptoms increases the likelihood of treatment resistance (Kornstein and Schneider 2001). In essence, incomplete MDD treatment predicts a protracted illness course for the patient and a higher burden on society.

4

Epidemiology

Prevalence

MDD is one of several depressive disorders affecting people across the world. The 2017 NIMH-funded National Survey on Drug Use and Health reported that "an estimated 14.5 million U.S. adults aged 18 or older had at least one major depressive episode with severe impairment. This number represented 5.7% of all U.S. adults" (National Institute of Mental Health 2023). This staggering prevalence estimate for severe depression places MDD among the most common illnesses affecting adults across the world and includes "an estimated 5 million adolescents aged 12 to 17 in the United States" who "had at least one major depressive episode." The annual prevalence estimate of an MDE in female adolescents towered over that of male adolescents, at 29.2% versus 11.5%, with only 40.6% of all U.S. adolescents receiving treatment (National Institute of Mental Health 2023).

Persistent depressive disorder (PDD), formerly known as dysthymic disorder, is a related depressive disorder involving milder symptoms and a more chronic course compared with MDD. DSM-5 (American Psychiatric Association 2013) grouped dysthymia with other forms of chronic depression into the more expansive category of PDD as a distinction from episodic, recurrent major depressive disorder (Schramm *et al.* 2020).

Unfortunately, patients with PDD may have as much functional impairment as those with MDD and tend to have a more refractory course compared with those with nonchronic depression. PDD commonly co-occurs with MDD in a phenomenon clinically known as double depression. The National Comorbidity Survey Replication estimated the annual prevalence of PDD (2001-2003) at 1.5% of all U.S. adults, with 49.7% of these individuals having severe impairment (Kessler *et al.* 2005).

Of note, problematic diagnostic limitations continue to plague the field as lack of validated biomarkers and reliance on narrative interviewing complicate diagnostic precision and reliability. The fact that two patients with MDD can exhibit highly divergent symptom profiles, illness courses, and degrees of disability contributes to the idea that MDD is likely a phenotypic endpoint of a genetically heterogeneous illness group with differential treatment response. This idea is supported by genome-wide association studies of MDD that identity more than 40 discrete genetic loci and more than 100 genetic variants, each of which represents a small risk factor (Gerring *et al.* 2019; Howard *et al.* 2019).

Risk Factors

There are multiple risk factors for MDD, including sex, genetic loading, age, childhood maltreatment, and other environmental factors and comorbid medical illnesses. In the prepubertal phase there is no meaningful sex difference in the prevalence of MDD, but the onset of puberty marks an approximately twofold increased risk for girls compared with boys, a consequence of hormonal changes from the reproductive cycle (Kessler *et al.* 1994). This risk elevation is sustained for most of the life cycle, with intersex MDD risk eventually returning to comparable rates after age 65 years (Bebbington *et al.* 2003). Curiously, sex does not appear to influence the rates of illness recurrence in MDD.

Genetic loading plays a key part in MDD transmission, with the average general heritability risk estimated at approximately 37% (Sullivan *et al.* 2000). Some evidence suggests even greater familial risk with early-onset and recurrent MDD subtypes (Klein *et al.* 2002; Weissman *et al.* 1984).

Age is also relevant to MDD risk. Prevalence rates are generally low until early adolescence, where there is a rapid escalation that softens as patients approach middle adulthood (Wilson *et al.* 2014). After a single MDE, longitudinal epidemiological studies reveal that approximately 50% of affected people will have a second episode (and likely more thereafter), typically within 5 years of the index episode. On average, affected people experience five discrete lifetime episodes (Wilson *et al.* 2014). Lastly, patients with early-onset MDD are more likely to experience a recurrent illness course throughout life, with incomplete interepisodic recovery, briefer asymptomatic periods, higher rates of relapse and recurrence, and more chronic episodes.

Despite substantial genetic risk, nongenetic factors explain ~ 60%-70% of the variance in MDD susceptibility. This risk is determined largely by the experience of childhood adversity and other stressors, including childhood sexual abuse, general trauma, limited social support, marital strain, and divorce (Kendler *et al.* 2002, 2006). Because these problems are not modifiable with psychotropic medication, the value of psychosocial treatment cannot be overstated.

As a final point, co-occurring medical conditions are a final contributor to MDD risk, likely via a combination of direct and indirect pathophysiological mechanisms. Prior research has established an association between MDD and coronary artery disease, congestive heart failure, myocardial infarction, stroke, diabetes, cancer, autoimmune diseases, Parkinson's disease, and dementia (Iosifescu *et al.* 2003). Based on this body of literature, it is clear that comorbid medical illness, especially in multiple organ systems, correlates with lower recovery rates, greater chronicity, and worse acute phase treatment outcomes. Furthermore, there is likely a bidirectional relationship between MDD and other medical illnesses whereby depression can be a cause or consequence of medical comorbidity (Ramasubbu *et al.* 2012).

Neurobiology of Depression

As mentioned previously, there is no known single etiological driver for MDD; rather, it is best viewed as a final common pathway of various pathophysiological mechanisms that each confer risk. That said, multiple distinct biological derangements are consistently observed in MDD.

Monoamine Deficiency Hypothesis

One of the longest-standing theories of depression pathophysiology is the monoamine deficiency hypothesis. This argues that a relative depletion of serotonin, norepinephrine, or dopamine in the CNS drives depressive pathology. In support of this theory, most pharmacological compounds that increase monoamine neurotransmission have demonstrated antidepressant efficacy (Belmaker and Agam 2008). Such compounds include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), heterocyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and others. However, antidepressant monotherapy remission rates are generally 30% or less depending on the level of treatment resistance; thus, other factors apart from monoamine deficiency are likely at play.

Among other relevant factors, alterations in stress hormone response, elevated proinflammatory cytokines, structural and functional brain abnormalities, circadian rhythm dysfunction, neurotrophic factors, and altered glutamate and GABA neurotransmission have all been implicated as risk factors in MDD (Hasler 2010).

Neuroendocrine Dysfunction and Stress Hormones

Corticotropin-releasing hormone is released by the hypothalamus in response to psychological stress. This induces subsequent pituitary secretion of adrenocorticotropin, which then stimulates the adrenal gland to release cortisol, a major stress hormone. Women generally show higher stress responsiveness than men, consistent with the greater MDD prevalence in women (Young 1998). Although psychological stress is considered a risk factor for MDD, the majority of depressed patients do not demonstrate significant hypothalamic-pituitary-adrenal (HPA) axis dysfunction (Belmaker and Agam 2008). Regardless, nonsuppression in the dexamethasone/corticotropin-releasing hormone test is a consistent indicator of elevated relapse risk for patients with MDD during clinical remission (Schule 2007). Curiously, among patients with MDD who demonstrate alterations in stress hormone secretion, childhood trauma appears to be more prominent (Heim *et al.* 2008). The more recent finding that epigenetic regulation of glucocorticoid receptors is associated with childhood abuse establishes one link between early life adversity and HPA axis dysfunction that increases MDD risk (McGowan *et al.* 2009). Chronic elevations in cortisol may also act as a mediator between MDD and various comorbid medical conditions including coronary artery disease and type 2 diabetes mellitus, further complicating the plight of depressed patients (Gold and Chrousos 1999).

Inflammation

Proinflammatory cytokines such as interleukin-1a, tumor necrosis factor-a, and interleukin-6 also increase MDD risk by activating the HPA axis and disrupting the central serotonin system (Dantzer *et al.* 2008). Cytokine release also produces "sickness behavior" with symptoms similar to neurovegetative signs in depression, such as fatigue, anhedonia, psychomotor retardation, and cognitive impairment (Hasler 2010). Interest in the depressogenic mechanism of inflammatory cytokines stems from clinical observations of patients receiving interferon for various medical conditions (e.g., hepatitis C virus) who ultimately developed depressive symptoms. The prevalence of depression in the context of exposure to recombinant interferon is estimated to be about 30% (Loftis and Hauser 2004). Although significant, the risk is not absolute, again supporting the theory that alignment of multiple risk factors is necessary for the phenotypic expression of an MDE. Finally, some clinical data suggest that inflammatory cytokines play a more significant role in certain subsets of patients with depression--in particular, those with comorbid medical conditions (Dantzer *et al.* 2008).

Genetics and Epigenetics

Scientific inquiry about genetic risk for MDD includes family, twin, and adoption studies. Conclusions from these studies consistently find MDD to be a familial disorder with genetic factors accounting for 30%-40% of the overall risk (Sullivan *et al.* 2000). Despite high confidence from these epidemiological studies about genetic risk in MDD, there is no single candidate gene responsible for this genetic risk burden. Genome-wide association studies of MDD have identified more than 40 relevant genetic loci with more than 100 independent genetic variants, each contributing slightly to overall risk (Gerring *et al.* 2019; Howard *et al.* 2019). Nongenetic factors account for the remainder of the risk, with childhood adversity, acute or chronic interpersonal challenges, lifetime trauma, limited or absent social support, marital strain, and divorce all having substantial negative impact (Kendler *et al.* 2002 [in women]; Kendler *et al.* 2006 [in men]). The negative impact of childhood adversity on MDD expression has been more recently explained by epigenetics, that is, the alteration of gene expression by processes that do not alter the underlying genetic code. Epigenetic changes include modification in gene expression via DNA methylation and acetylation, and evidence suggests that these processes may contribute to intergenerational transmission of trauma (Lippard and Nemeroff 2020). With such a substantial proportion of MDD risk being environmentally mediated, epigenetically or otherwise, there exists significant opportunity for prevention via psychosocial interventions because psychotherapy tends to have a broader, more generalized effect compared with pharmacotherapy.

Treatment Options

Pharmacotherapies

Antidepressants are an important therapeutic option in the holistic treatment of MDD. Whereas individual antidepressant agents and their associated pharmacological profiles are addressed elsewhere in this text (see Chapters 10 through 24), this chapter reviews practical considerations in the selection and optimization of treatment and the assessment of antidepressant response while also covering nonpharmacological treatments for MDD and other depressive disorders.

Choosing the Initial Antidepressant

The 2016 Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Adults with Major Depressive Disorder recommend second-generation antidepressants (SSRIs, SNRIs, mirtazapine, bupropion, vortioxetine, agomelatine) as appropriate first-line treatment interventions for MDEs of moderate or greater severity (Kennedy *et al.* 2016). Ideally, severity is determined by the degree of functional impairment caused by the neurovegetative symptom burden as measured by a validated depression rating scale, either self-or clinician-administered. For mild depressive episodes, the 2016 CANMAT MDD Guidelines recommend "psychoeducation, self-management, and psychological treatments" (Kennedy *et al.* 2016, p. 541); therefore, pharmacotherapy for MDD is typically reserved for MDEs of moderate or greater severity.

A large systematic review and network meta-analysis evaluating efficacy and acceptability of 21 first-and second-generation antidepressants found all were superior to placebo, with limited comparative efficacy differences (Cipriani *et al.* 2018). Therefore,

initial antidepressant selection for medication-naive patients is based largely on the anticipated side-effect profile. SSRIs are typically favored in this context because of superior tolerability profiles compared with SNRIs, TCAs, and MAOIs, along with relative safety, even in the context of overdose (Anderson 2000; Barbey and Roose 1998; Nemeroff *et al.* 2008). SSRI exposure (along with most other serotonergic antidepressants) does involve a well-known risk of sexual dysfunction, which can be intolerable to some patients and precipitate discontinuation. Identifying the true incidence of SSRI-mediated sexual dysfunction is complicated by the presence of preexisting depression-mediated sexual dysfunction (Montejo *et* *al.* 2018). Two European cross-sectional studies evaluating the prevalence of SSRI or SNRI sexual dysfunction reported 27%-65% of female and 26%-57% of male patients experienced either new-onset sexual dysfunction or worsening of preexisting symptoms (Williams *et al.* 2006, 2010). Luckily, there are antidepressant alternatives with minimal risk of sexual dysfunction. One meta-analysis found rates of treatment-emergent sexual dysfunction from bupropion, mirtazapine, and nefazodone to be no higher than those of placebo (Serretti and Chiesa 2009). These agents may be preferable for some patients.

Numerous other factors are relevant to antidepressant selection, of which a full discussion exceeds the scope of this chapter. Ideally, a decision is reached after a thoughtful conversation between the clinician and patient that includes a review of diagnosis, illness education, review of past treatment history and response, medical considerations (comorbidities, drug-drug interactions), risks versus benefits of various antidepressant options in the current context, patient preference, and other ancillary factors. Table 48-1 lists important considerations relevant to antidepressant selection (Kennedy *et al.* 2016).

TABLE 48-1. Factors to consider in selecting an antidepressant

Patient factors	Medication factors
* Clinical features and dimensions	* Comparative efficacy
* Comorbid conditions	* Comparative tolerability (potential side effects)
* Response and side effects during previous use of antidepressants	* Potential interactions with other medications
* Patient preference	* Simplicity of use

Source. Reprinted from Table 4 (p. 543) in Kennedy SH, Lam RW, McIntyre RS, et al.; CANMAT Depression Work Group: "Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults With Major Depressive Disorder. Section 3: Pharmacological Treatments." *The Canadian Journal of Psychiatry* 61(9):540-560, 2016. Copyright 2016, The Authors. Reprinted by permission of SAGE Publications.

Patient factors	**Medication factors**
	* Cost and availability

Source. Reprinted from Table 4 (p. 543) in Kennedy SH, Lam RW, McIntyre RS, et al.; CANMAT Depression Work Group: "Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults With Major Depressive Disorder. Section 3: Pharmacological Treatments." *The Canadian Journal of Psychiatry* 61(9):540-560, 2016. Copyright 2016, The Authors. Reprinted by permission of SAGE Publications.

Of note, despite the relatively comparable efficacy of antidepressants for MDD as a whole, several major depressive subtypes warrant consideration of unique therapeutic approaches. For example, MDD with psychotic features (MDE plus delusions or hallucinations) is unlikely to respond to antidepressant monotherapy; rather, the combination of an antidepressant plus antipsychotic medication, or a course of electroconvulsive therapy (ECT), is superior (Charney and Nelson 19981). MDD with atypical features ("atypical depression"), characterized by extreme mood reactivity, rejection sensitivity, hyperphagia, hypersomnia, and leaden limb paralysis, responds more robustly to oral irreversible MAOIs than to TCAs (Henkel *et al.* 2006). MDD with seasonal pattern, known formerly as seasonal affective disorder, may benefit from routine antidepressant therapy or bright light therapy (BLT) during the fall and winter, with early morning BLT increasing the chance of remission (Maruani and Geoffroy 2019). Lastly, PDD, a DSM-5 diagnosis capturing multiple chronic depressive phenotypes, may require longer periods of treatment, with medication or psychotherapy, proportional to the degree of chronicity (Schramm *et al.* 2020). A network meta-analysis of pharmacology for PDD showed SSRIs, moclobemide, imipramine, ritanserin, and amisulpride to be more efficacious than placebo, with only fluoxetine proving less efficacious (Kriston *et al.* 2014).

Assessing and Optimizing Treatment Response

The goal of MDD treatment is to achieve full symptomatic remission with resolution of depression-mediated functional disability. This goal is important because chronic depression, defined as incomplete remission between MDD episodes or persistent symptoms for 2 or more years, increases the likelihood of treatment resistance and correlates with more severe functional impairment, more frequent suicide attempts, and worse prognosis (Kornstein and Schneider 2001). Once a patient achieves remission, the clinical focus shifts to prevention of recurrent episodes because MDD and other depressive disorders are well known to recur over the life cycle, with most patients experiencing multiple lifetime episodes (Hollon *et al.* 2002).

After selecting the initial antidepressant, the clinician should confirm the mean dosage correlating with efficacy in established clinical outcome trials and set expectations for titration to that target dosage. Lower starting dosages are commonly initiated to facilitate tolerability, but remaining at a subtherapeutic dosage may not be sufficient to evaluate benefit and risk, extending the time spent ill. For this reason, patient education about antidepressant trial adequacy is key, this being defined as exposure to a minimum effective antidepressant dosage for an adequate duration of time. An adequate antidepressant trial is generally considered to be 6-8 weeks at or above an established mean effective dosage. Inadequate antidepressant trials play a key role in negative outcomes and increased health care costs (Weilburg *et al.* 2003).

In the setting of an adequate antidepressant trial, the clinician should maintain awareness of four possible outcomes: nonresponse (0%-25% improved), partial response (25%-50% improved), response (> 50% improvement), and remission (full functional recovery). These outcomes are best defined via the combination of a clinical interview and use of a validated depression symptom severity rating instrument, either self-administered or clinician administered. Depending on the outcome of the antidepressant trial, the clinician will respond as is appropriate.

In the case of nonresponse to an initial antidepressant trial, the clinician must first rule out causal factors of pseudoresistance. Pseudoresistance, as the name implies, is the perception of treatment resistance in the setting of inaccurate diagnosis, trial inadequacy, or unrecognized treatment-interfering comorbidity (medical or psychiatric), including substance abuse (Kornstein and Schneider 2001). Table 48-2 summarizes various reasons for poor response to antidepressant therapy (Cleare *et al.* 2015; Culpepper *et al.* 2015). If pseudoresistance is ruled out, it is most prudent to switch to another antidepressant, either within the same class (e.g., SSRI to alternative SSRI) or in a different class (e.g., SSRI to SNRI). Various studies have attempted to clarify whether out-of-class switch strategies are superior to within-class switches. For example, a 2008 meta-analysis of four clinical trials (1,496 pooled subjects) revealed a small statistical advantage for depressed SSRI nonresponders who switched to a non-SSRI (bupropion, mirtazapine, venlafaxine) versus a second SSRI (28% remission vs. 23.5%) (Papakostas *et al.* 2008). In this study, the number needed to treat (NNT) was calculated at 22, meaning 22 SSRI nonresponders would have to be switched to a non-SSRI to obtain one additional remitter, a slight advantage at best.

TABLE 48-2. Reasons for poor response to antidepressant pharmacotherapy

Poor adherence to medication (consider therapeutic drug monitoring, where appropriate)
Inadequate dosage (or serum value in the case of selected TCAs)
Inadequate duration of treatment
Inaccurate diagnosis (e.g., secondary depression, bipolar I or II depression)
Undiagnosed psychiatric symptoms (e.g., psychotic or atypical features) or comorbidity (e.g., substance use disorder, personality disorder, anxiety disorder)
New or worsening medical comorbidities

Note. TCAs = tricyclic antidepressants.
Source. Cleare *et al.* 2015; Culpepper *et al.* 2015.

Drug-drug interactions (particularly concomitant medications that may worsen depressive symptoms, aggravate antidepressant side effects, or lead to excessively rapid metabolism of the antidepressant)

Undiagnosed psychosocial factors that are prolonging depressive symptoms

Note. TCAs = tricyclic antidepressants.
Source. Cleare *et al.* 2015; Culpepper *et al.* 2015.

Should a patient respond, either partially or fully, to an adequate antidepressant trial, it is important to continue to push for remission because of the elevated relapse rates and higher risk for persistent residual functional impairment in partially improved depressed patients (Culpepper *et al.* 2015). There are various treatment maneuvers to consider in this context, including antidepressant dosage optimization, adjunctive therapy (i.e., adding another medication or psychotherapy), or switching. Stepwise dosage optimization is typically preferred in the setting of good antidepressant tolerance and clear incremental benefit from prior dosage increases. Adding psychotherapy is preferred in the setting of medication intolerance, patience preference, or scenarios in which depressive symptoms are difficult to distinguish from a patient's response to psychosocial stressors. Adjunctive pharmacotherapy involves adding a second drug, either a second antidepressant (referred to as *combination therapy*) or a non-antidepressant such as an atypical antipsychotic or lithium (referred to as *augmentation therapy*).

Adjunctive therapy with a second antidepressant typically involves selecting a second agent with a different mechanism of action. Historically, clinicians have theorized that combining medications that increase central monoamine availability (i.e., serotonin, norepinephrine, dopamine) via differential mechanisms might be superior to single monoamine modulators such as SSRIs. However, efficacy data are lacking in this regard. A trial by Stewart *et al.* (2014) compared initial treatments for MDD by randomly assigning 255 subjects either to escitalopram or bupropion monotherapy or to combination escitalopram/bupropion, with no reported advantage for any treatment group at 12 weeks. A similar study by Rush *et al.* (2011) compared escitalopram monotherapy and combination therapy with either escitalopram/bupropion or venlafaxine/mirtazapine for 665 patients with moderate to severe MDD. Response and remission rates did not differ at either 12-week or 7-month endpoints; however, tolerability was worse for both combination therapy groups. Overall, the evidence supporting antidepressant combination therapy remains weak, and this approach clearly cannot be recommended at treatment initiation (Kennedy *et al.* 2016). A practical role for combination antidepressant therapy may exist in certain clinical scenarios in which a second antidepressant with a novel mechanism of action is added to improve isolated target symptoms in addition to mood (e.g., bupropion augmentation for fatigue, mirtazapine for insomnia).

Adjunctive therapy with atypical antipsychotics has a stronger evidence base than combination antidepressant therapy. A systematic review by Spielmans *et al.* (2013) examined 14 short-term trials of aripiprazole, olanzapine/fluoxetine combination (OFC), quetiapine, and risperidone. All four agents had a statistically significant effect on remission, with an NNT of 9 for aripiprazole, quetiapine, and risperidone. OFC had an NNT of 19, a finding of more questionable clinical relevance. Adverse effects were present, including akathisia (aripiprazole), sedation (quetiapine, OFC, and aripiprazole), metabolic derangement (quetiapine and OFC), and weight gain (all four agents, particularly OFC). Overall, the benefit of atypical antipsychotic augmentation was deemed to be small to moderate, with no clear benefit with regard to quality of life or functional impairment.

Adjunctive therapy with lithium is another long-standing strategy to achieve remission from an MDE. A systematic review and meta-analysis by Nelson *et al.* (2014) examined lithium augmentation of TCAs as well as second-generation antidepressants. The study revealed that lithium augmentation was superior to placebo augmentation of TCAs or second-generation antidepressants, with a pooled OR of 2.89 and remission rate of 46.1% in the lithium augmentation groups, compared with 25.4% in the placebo augmentation group. The World Federation of Societies of Biological Psychiatry guidelines for MDD state that "lithium augmentation should be administered for 2-4 weeks in order to allow assessment of the patient's response. The recommended lithium serum target levels are 0.6 to

0.8 mmol/L. In case of response, lithium augmentation should be continued for at least 12 months" (Bauer *et al.* 2013). Lastly, lithium is well known to reduce the odds of suicide completion, a finding that originated from bipolar outcome studies (Grof and Muller-Oerlinghausen 2009). A meta-analysis by Guzzetta *et al.* (2007) of lithium exposure in 329 pooled patients with MDD found the overall risk of suicide completions and attempts to be 88.5% lower in patients taking lithium than in patients without lithium exposure. For this reason, lithium augmentation should be considered for depressed patients struggling with persistent suicidal ideation.

Finally, thyroid hormone augmentation with triiodothyronine (T_3) is yet another augmentation strategy for MDD. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial included T_3 augmentation versus lithium augmentation at level 3, and reported a 24.7% remission rate (nonsignificant trend toward superiority) and better relative tolerability with T_3 (Gaynes *et al.* 2009). A review by Connolly and Thase (2011) concluded that T_3 augmentation has efficacy for TCA nonresponders, with an NNT "essentially equivalent to that of lithium." However, the authors also noted that there remains a paucity of positive randomized controlled trials (RCTs) supporting the routine use of T_3 by euthyroid patients. For this reason, screening patients for high normal thyroid-stimulating hormone levels or known subclinical hypothyroidism with co-occurring depressive symptoms (especially treatment-resistant depression [TRD]) may prove fruitful. Adding either T_3 or thyroxine (T_4) with a target thyroid-stimulating hormone level below 2.5 mIU/mL, perhaps < 2 mIU/mL, may increase rates of remission (Cohen *et al.* 2018).

Managing Treatment-Resistant Major Depressive Disorder

An unfortunate reality in the treatment of major depressive disorder is that approximately one-third of patients do not achieve remission after two adequate antidepressant interventions with drugs from different classes. This fact was well highlighted in the STAR*D trial, the largest National Institutes of Health-funded depression trial in history, and serves as the working definition of TRD (Gaynes *et al.* 2009). After two failed antidepressant interventions in STAR*D, including multiple antidepressant classes and cognitive-behavioral therapy, remission rates dropped from 31% to 14%. This pivotal point in treatment predicts not only lower remission rates with subsequent interventions but also high rates of relapse and greater medication intolerance (Conway *et al.* 2017; Rush *et al.* 2006). Additionally, TRD is associated with higher risk for overall psychiatric and medical comorbidity, increased health care costs, and elevated risk of death from medical illness and suicide (Greden 2001).

For patients struggling with presumed TRD, it is first important to ensure that pseudoresistance has been ruled out to the extent possible. Assuming that practical factors limiting response have been reviewed (see Table 48-2), it is important for the clinician to carefully review the treatment history, examining it for novel therapeutic interventions that have not been previously explored. This might involve a novel trial with a TCA or MAOI; augmentation with an atypical antipsychotic, thyroid hormone, or lithium; combination therapy with another antidepressant; or the addition of evidence-based psychotherapy, neuromodulation, or, in select cases, ketamine or esketamine therapy. Of all these options, ECT remains the most powerful and effective treatment option for TRD and is reviewed in the next section.

Intravenous ketamine infusion has shown potential in the acute relief of depressive symptoms and suicidal ideation, so it is of therapeutic interest in TRD. A trial comparing single, repeated, and maintenance ketamine infusions for TRD showed that a single ketamine infusion, versus an active midazolam comparator, correlated with significantly greater depressive symptom reduction, peaking at 24 hours and abating by day 7 (Phillips *et al.* 2019). All subjects relapsed before entering the repeated infusion phase, with subsequent restoration of antidepressant efficacy upon resuming thrice-weekly ketamine infusions. Although benefit was maintained in ketamine responders over the next 30 days with weekly maintenance infusions, uncertainty remains about long-term toxicity and abuse potential, given that ketamine has been shown to modulate the endogenous opioid system in addition to antagonizing *N*-methyl-D-aspartate (NMDA) receptors (Williams *et al.* 2018).

Intranasal esketamine, the *(S)*-isomer of racemic ketamine, was approved by the FDA for the treatment of TRD in 2019, with efficacy demonstrated in one Phase III trial comparing esketamine plus a novel antidepressant versus placebo plus a novel antidepressant (Popova *et al.* 2019). Although exciting in some respects, mainly because of the relative ease of outpatient administration, the approval was unusual in that the FDA typically requires two positive Phase III trials before approval. In two prior Phase III studies, esketamine failed to separate from placebo, and despite showing Montgomery-Asberg Depression Rating Scale (MADRS) change scores similar to those in the pivotal study that compelled the FDA to approve esketamine, the effect sizes were notably in the mild range (Schatzberg 2019). Other noteworthy criticisms have been raised about the early esketamine trials, including a published commentary by Turner (2019), who called attention to an "arguably lax regulatory definition" of TRD that included subjects with two within-class (i.e., SSRI) drug failures, a modest 4-point MADRS reduction, enrichment of the randomized withdrawal trial (3,003) with esketamine responders, an outlier trial site in Poland with "a 100% rate of placebo arm relapses," and a standardized mean difference of change in MADRS score inferior to those of aripiprazole and quetiapine augmentation. Compounding these concerns about the fidelity of the outcome data, there were three patients who completed suicide in the active intervention arm (compared with zero in the placebo group), one fatality by motorcycle accident, and two other deaths from cardiovascular complications (U.S. Food and Drug Administration 2019). Although none of the six trial deaths were directly attributed to esketamine, the mortality rate in the trial was worrisome. Overall, despite esketamine's widespread use for TRD, its role remains unclear, especially because long-term exposure data are still being collated to evaluate for negative consequences of chronic exposure.

Somatic Therapies

Somatic therapies are nonpharmacological treatments that directly stimulate the brain in an effort to reduce psychiatric symptoms. ECT is the oldest and most efficacious form of neurostimulation, whereby an electrical stimulus is applied to the brain, with subsequent induction of a brief generalized seizure. Although ECT is classically used in the context of multiple antidepressant failures, it can be used as a first-line therapy in certain situations including imminent suicidality, malnutrition, severe postpartum depression, or agitated psychosis (American Psychiatric Association Task Force on Electroconvulsive Therapy 2001; Kellner *et al.* 2012). Patient preference for ECT should also be considered because certain people may prefer to use ECT if it has been effective for prior depressive episodes. ECT response rates are very high, typically in the 70%-80% range, and it is clearly superior to pharmacological interventions, although it is more invasive and requires anesthesia, similar to other brief medical procedures (Milev *et al.* 2016). Despite substantial advances in ECT technique, such as unilateral electrode placement and ultrabrief-pulse-width stimulation, tolerability concerns, namely anterograde and retrograde amnesia, are barriers to early and widespread use. Thus, ECT is commonly used at a very late stage in MDD, a practice that has been called into question given ECT's documented superiority compared with other therapies (Beale and Kellner 2000).

Repetitive transcranial magnetic stimulation (rTMS) is less invasive form of brain stimulation that can be safely performed on an outpatient basis without anesthesia. Traditional rTMS sends pulses of electrons through a "figure of eight" copper wire coil to create trains of strong (1-2.5 tesla) magnetic pulses that penetrate the cortex up to 2 cm in depth, resulting in underlying neuronal depolarization. Both high-frequency "excitatory" and low-frequency "inhibitory" rTMS delivered to the left and right dorsolateral prefrontal cortex, respectively, have demonstrated efficacy in treating MDD, although only high-frequency rTMS to the left dorsolateral prefrontal cortex is FDA approved for patients with MDD after a single antidepressant failure (Berlim *et al.* 2014). A standard rTMS course delivers a minimum of 3,000 pulses per session, 5 days per week over 4-6 weeks, for a total of 20-30 sessions (McClintock *et al.* 2018). The lack of anesthesia and the ability to safely drive immediately after the procedure make rTMS an attractive alternative to more invasive brain stimulation procedures, such as ECT. However, rTMS response and remission rates resemble those of antidepressant trials and may not be sufficient for severe, refractory depression (Grammer *et al.* 2015). Recent developments in TMS have led to the approval of a new protocol involving a modified stimulation pattern, intermittent theta burst stimulation (iTBS), that reduces delivery time from 15-45 minutes to 1-3 minutes (Milev *et al.* 2016). iTBS, now also FDA approved for TRD, was shown to be noninferior to traditional rTMS, so the reduced delivery time is especially attractive to clinicians because more patients may be treated in a single working day (Blumberger *et al.* 2018). Burgeoning research on iTBS, including multiple daily treatments and functional connectivity-guided functional MRI targeting, may shorten iTBS treatment courses from weeks to days and optimize remission rates even further (Cole *et al.* 2020).

Vagus nerve stimulation (VNS) is an invasive therapy for TRD that was FDA approved in 2005 for chronic or recurrent depression that has not adequately responded to four or more adequate antidepressant treatments (American Psychiatric Association 2009). VNS involves surgically implanting a small lead wire in the neck, attached to the afferent fibers of the left vagus nerve, and stimulating it with an implanted pulse generator placed subcutaneously in the chest or axilla. A 5-year open-label, nonrandomized, observational registry study of patients with TRD compared VNS versus treatment as usual, demonstrating a significantly higher 5-year cumulative MADRS response rate (67.6%) in the VNS versus the treatment-as-usual group (40.9%) (Aaronson *et al.* 2017). This long-term trial highlighted the importance of long-term stimulation as opposed to short-term stimulation, which is less effective. The average study patient had experienced an average of 8.2 depression treatment failures, so VNS therapy may offer hope for functional improvement in the setting of profound TRD, although the surgical invasiveness and specialized skills needed to implant and program VNS are limiting factors.

Deep brain stimulation involves the surgical implantation of paired electrodes into specific bilateral brain structures (i.e., subcallosal cingulate, ventral capsule/ventral striatum, medial forebrain bundle) in an effort to modulate the neural network implicated in major depressive disorder (Drobisz and Damborska 2019). The electrodes are programmed to deliver small electrical pulses to the target areas via an implanted pulse generator in an effort to positively influence mood network dysfunction noted in prior imaging studies. Deep brain stimulation outcomes for TRD have been mixed in the setting of variable stimulation targets, problems with study design and surgical planning, and incomplete understanding of brain networks implicated in TRD on a general and individual level (Filkowski and Sheth 2019). However, improvements in imaging techniques, individualized targeting, and a shift to a "systems/circuits perspective" in psychiatric neuroscience research create promise for this intervention (Widge *et al.* 2018).

BLT is a first-line therapy for MDD with seasonal pattern (formerly known as seasonal affective disorder) and may have a role as a monotherapy or combination therapy

along with an antidepressant in nonseasonal MDD (Lam *et al.* 2016). Morning administration of 30 minutes of BLT with a 10,000-lux light box affords the best chance of remission and may also be efficacious for antepartum and chronic depression (Pail *et al.* 2011). The nonpharmacological nature of BLT is an attractive option for patients who are demoralized by numerous failed antidepressant trials or have exposure concerns such as pregnancy.

In summary, ECT remains the most efficacious somatic therapy for MDD and TRD, but ongoing work in brain stimulation research adds hope for less invasive and more tolerable treatment options for the most treatment-resistant patients. Earlier consideration of neuromodulation treatment is an important option, if not a cultural shift in the field, as it is critical to combat symptoms aggressively before they become chronic and treatment resistant.

Psychotherapies

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) was developed by Aaron Beck as a time-limited alternative to open-ended psychoanalytic psychotherapy. By design, CBT was structured for compatibility with RCT investigation and subsequently has been evaluated in numerous RCTs. The aim of CBT is to teach patients how to actively monitor themselves for automatic thoughts, identifying and reformulating extreme or negative thoughts and assumptions about one's self, situation, or future that correlate with unpleasant feelings and unhelpful behaviors. Behavioral interventions are embedded in the therapy as "homework" exercises designed to promote healthy engagement and behavioral activation and minimize withdrawal. For the treatment of acute depression, a meta-analytic evaluation of pooled outcome trials found a medium effect size for CBT relative to a variety of control conditions, with an NNT of 2.75 (Driessen and Hollon 2010). A major advantage of CBT in comparison with pharmacotherapy is the apparent enduring protective effect against relapse and recurrence after the end of active treatment (Lynch *et al.* 2010). Combination therapy with CBT plus antidepressants is known to be superior to pharmacotherapy alone irrespective of the psychotherapy modality (Cuijpers *et al.* 2014).

Interpersonal Therapy

Interpersonal therapy (IPT) was developed by Dr. Gerald Klerman and colleagues in the 1970s, initially as part of a study evaluating the efficacy of a TCA, with and without psychotherapy, for the maintenance treatment of unipolar depression in outpatients (Weissman 2020). Dr. Klerman's team defined a time-limited therapy with a clearly defined procedure (manual) so that psychotherapists could be trained to deliver it with high reliability across various settings. IPT focuses on four important areas: grief, role transitions, role disputes, and interpersonal deficits. In a meta-analysis by

Cuijpers *et al.* (2016), IPT had moderate to large effects compared with other psychotherapies in the treatment of patients with acute-phase depression, preventive effects against development of an MDE in patients with subclinical depressive symptoms, and noninferiority compared with CBT. A possible disadvantage of IPT compared with CBT is that IPT may be effective for relapse prevention only while it is continued (Frank *et al.* 2007).

Mindfulness-Based Cognitive Therapy

Mindfulness-based cognitive therapy (mbCT) is a newer psychotherapy that integrates selected elements of CBT for depression with the application of mindfulness meditation (van der Velden *et al.* 2015). Patients are encouraged to adopt a new way of relating to thoughts and feelings, placing little emphasis on changing specific cognitions, and findings from multiple research trials suggest efficacy for relapse prevention for patients with recurrent depression (Sipe and Eisendrath 2012). A meta-analytic review of pooled mbCT studies revealed large, clinically significant effects for mbCT in treating depression, with maintenance of gains at follow-up and smaller attrition rates in comparison with other cognitive and behavioral therapies (Khoury *et al.* 2013). There is also preliminary evidence of mbCT's efficacy in treatment-resistant depression (Eisendrath *et al.* 2016).

Other Psychotherapies

Various other psychotherapy modalities have been evaluated for patients with MDD, including behavioral activation, short-term psychodynamic psychotherapy, acceptance and commitment therapy, motivational interviewing, Cognitive Behavioral Analysis System of Psychotherapy, and self-guided treatments including bibliotherapy and computer-based delivery platforms for psychotherapy (Lampe *et al.* 2013; Parikh *et al.* 2009). Although empirical evidence exists for CBT and IPT, an American Psychological Association resolution from August 2012 recognized that

> comparisons of different forms of psychotherapy most often result in relatively nonsignificant difference, and contextual and relationship factors often mediate or moderate outcomes. These findings suggest that 1) most valid and structured psychotherapies are roughly equivalent in effectiveness and 2) patient and therapist characteristics, which are not usually captured by a patient's diagnosis or by the therapist's use of a specific psychotherapy, affect the results. (American Psychological Association 2012)

Adjunctive Treatments

Complementary and Alternative Medicine Approaches

There are several complementary and alternative medicine approaches for the treatment of major depressive disorder. In general, these agents have not been studied in large-scale, well-powered randomized controlled clinical trials, as is required by the FDA for approval for any psychiatric indication. Some small trials have found evidence of efficacy, and others have not. Preparations of St. John's wort (SJW, *Hypericum perforatum*), a perennial flowering herb naturally occurring in temperate zones across the globe, have been used to treat depression since the 1980s (Nahas and Sheikh 2011). SJW inhibits the reuptake of serotonin and modifies levels of dopamine, norepinephrine, GABA, and other neurotransmitters (Shelton 2009). A 2008 Cochrane Review by Linde *et al.* (2008) confirmed the efficacy of SJW for mild to moderate depression, although care must be taken to not combine SJW with other serotonergic agents, particularly serotonin-modulating antidepressants (SSRIs, SNRIs, TCAs, MAOIs), because of the risk of serotonin syndrome.

Various nutraceuticals (pharmaceutical-grade nutrients) have also been studied as augmentation therapy to traditional antidepressants. In a 2016 meta-analysis by Sarris *et al.* (2016), primarily positive results were found for replicated studies testing *S*-adenosylmethionine, methylfolate, omega-3 polyunsaturated fatty acids (primarily eicosapentaenoic acid or ethyl eicosapentaenoic acid), and vitamin D. Since then, several failed trials with these agents have appeared.

Lifestyle Interventions

The routine psychiatric care of individuals with MDD includes recommendations for lifestyle modification. The optimization of physical activity (particularly with aerobic exercise), healthy dietary modification, regulation of one's sleep-wake cycle, incorporation of mindfulness meditation practice, and the elimination of recreational substance use (including alcohol and nicotine) have all been shown to be beneficial in addition to standard depression treatment (Sarris *et al.* 2014).

Conclusion

Evolution in the scientific understanding of the pathophysiology and treatment of major depressive disorder continues to progress; however, in many ways, advances in genetic and epigenetic research and neuroimaging techniques add even more complexity to the overall picture of this complex array of illness phenotypes. The field is fortunate to have a large treatment armamentarium including numerous antidepressants and various psychotherapy modalities, but despite these tools, a substantial proportion of patients do not receive adequate care or improve after first-or second-line therapies. Because the majority of mental health care in the United States occurs in the primary care setting, it is important to educate primary care clinicians in the basics of psychiatric diagnosis, measurement-based care, and adequate first-line psychopharmacology for depression, particularly because mental health specialists are in short supply. For patients experiencing any degree of treatment resistance, it remains critical for psychiatrists and other mental health clinicians to thoroughly understand the full menu of treatment options that exist to aggressively pursue remission, or else the risk of chronic, disabling disease remains unacceptably high.

For patients who respond to initial therapy but do not experience symptom remission, a full effort should be exerted to effect a complete remission. This effort should include consideration of aggressive antidepressant dosage optimization, switching to a novel antidepressant class, or initiating adjunctive therapy with other antidepressants, lithium, thyroid hormone, atypical antipsychotics, or psychotherapy. The addition of rTMS or iTBS is a relatively new, safe, and tolerable neuromodulation option for moderate depression after a single failed antidepressant trial. For patients with TRD, switching to an older antidepressant class (including TCAs and MAOIs), cautious consideration of ketamine, and referral for ECT are prudent yet seriously underused strategies.

Looking forward, active research in the domains of ketamine preparations and NMDA antagonists, psychedelic compounds, high-dose iTBS, and other novel brain stimulation methods confer hope for even more efficacious therapeutic tools. This combined with translational research from evolving neuroimaging techniques sets the stage for an exciting time in science and, hopefully, a future era of less depressive disease.

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CHAPTER 49

Treatment of Bipolar Disorder

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In this chapter, we review treatment options for bipolar disorder, drawing primarily from published randomized, placebo-controlled trials. When such data were lacking, we developed approaches based on results from open trials, naturalistic studies, and expert consensus guidelines. The treatment of bipolar disorder in youth is addressed separately in this textbook (see Chapter 60, "Treatment of Child and Adolescent Disorders," by Wagner and Pliszka).

Although optimal treatment for bipolar disorder includes both medical and nonmedical components (e.g., psychotherapy), effective psychopharmacology is a necessary and required therapeutic backbone of care. No substantive evidence exists to suggest that bipolar disorder can be managed successfully over time simply with psychotherapy or alternative nonmedical approaches. Consequently, the primary focus of this chapter is on psychopharmacology.

As described by Strakowski *et al.* (2020), in order to create an organizational structure geared toward providing the best treatment approaches, we present pharmacological treatments related to 1) the prevention of affective episodes (so-called maintenance therapy) and 2) the treatment of specific affective phases of illness. We are not suggesting that these phases are managed independently. Unlike some psychiatric conditions, in which managing individual symptoms or symptom clusters is the primary approach, in bipolar disorder we recommend first aggressively treating the *diagnosis*, after which addressing individual bothersome symptoms may be warranted. This approach is supported by increasing evidence that the most effective mood-stabilizing (maintenance) drugs tend to be first-line treatments for acute affective episodes. Nonetheless, clinicians must manage acute affective episodes, so we provide approaches for these events as well.

Maintenance Treatment of Bipolar Disorder

Bipolar disorder is defined by the occurrence of mania (type I) or hypomania plus depression (type II). Mania is perhaps the most predictive syndrome, because once it occurs, more than 90% of individuals develop a recurring lifelong affective illness (Goodwin and Jamison 2007). Because of the high risk of recurrence and morbidity associated with mood episodes and interepisode symptoms, maintenance treatment is usually recommended after a single manic episode and certainly after a second major affective episode (Hirschfeld *et al.* 2002). The goals of maintenance treatment include preventing recurrence of acute affective episodes, minimizing interepisode symptoms, optimizing psychosocial function, and preventing suicide (Keck and McElroy 2017). Although acute episodes may initially respond to a single medication, over the longer term and to achieve and sustain optimal recovery, combinations of medications plus psychotherapy are often required. As we have discussed elsewhere, however, even with the likelihood of requiring combination therapy, use of more than three daily psychotropic medications should seldom be necessary--and, in the rare cases where needed, should be prescribed thoughtfully (Strakowski *et al.* 2020).

Lithium

Lithium is the most extensively studied treatment of bipolar disorder in general and relapse prevention specifically. It is FDA approved for treatment of acute mania and relapse prevention in bipolar disorder. Randomized, placebo-controlled trials conducted in the 1960s and 1970s established that lithium provides a fourfold lower risk of relapse than placebo through at least 1 year (Keck *et al.* 2000). More recent studies continue to support these findings that lithium is superior in efficacy to placebo in preventing relapse into mania for as long as 18 months (e.g., Bowden *et al.* 2003; Calabrese *et al.* 2003). Moreover, large-scale, long-term follow-up studies from European lithium clinics, and decades of clinical experience, further support its long-term effectiveness (e.g., Felber *et al.* 2018; Schou 2001). Lithium prevents both manic and depressive episodes and, perhaps uniquely, decreases suicidality (Beynon *et al.* 2009; Muller-Oerlinghausen *et al.* 2005).

Unlike most other treatments, lithium is best managed by carefully monitoring serum levels. The optimal maintenance serum concentration is really not firmly established. Clinical practice and some research suggest that lower concentrations may be acceptable during maintenance than those used when managing acute mania (Malhi *et al.* 2017). However, Gelenberg *et al.* (1989) and Keller *et al.* (1992) found that levels of 0.4-0.6 mEq/L were associated with a two-to threefold increased relapse rate, and greater likelihood of subsyndromal symptoms, compared with levels of 0.8 mEq/L or higher. However, Perlis *et al.* (2002) reanalyzed the Gelenberg *et al.* (1989) study and found that abrupt drops in serum lithium levels, whether due to random reassignment or due to nonadherence, were the most powerful predictors of relapse, rather than serum levels per se. Unfortunately, side-effect risks are typically directly correlated with serum concentrations, so balancing these two competing needs of effective long-term treatment requires careful communication with the treated individual and diligent clinical oversight. The optimal lithium level will prevent relapse while minimizing both subsyndromal symptoms and bothersome side effects; this dosing may vary with symptoms over time and typically requires diligent long-term course-of-illness documentation to determine the best approach for each treated individual.

Common side effects associated with acute treatment with lithium include nausea, vomiting, tremor, somnolence, weight gain, and the perception of cognitive slowing. Lithium may interfere with thyroid function and exacerbate renal disease; consequently, thyroid and renal function must be regularly monitored during long-term lithium administration.

Antiepileptics

Although several antiepileptic (anticonvulsant) medications are commonly used for treating bipolar disorder, long-term relapse prevention studies are relatively few, and only *lamotrigine* is FDA approved for maintenance therapy in bipolar disorder. Two large 18-month double-blind, placebo-controlled relapse prevention trials comparing lamotrigine (200-400 mg/day) with lithium (0.8-1.1 mEq/L) found that lamotrigine, but not lithium, was superior to placebo in preventing depressive episodes (Bowden *et al.* 2003; Calabrese *et al.* 2003). In contrast, lithium, but not lamotrigine, was superior to placebo in preventing manic episodes. However, in a recent meta-analysis of both lamotrigine and lithium for relapse prevention, Oya *et al.* (2019) demonstrated that both lithium and lamotrigine were superior to placebo for reducing relapse into any mood episode, with lithium demonstrating greater numerical superiority overall. Finally, Calabrese *et al.* (2000) conducted a 6-month placebo-controlled relapse prevention study of lamotrigine (mean dosage = 288 mg/day) in 182 patients with rapid-cycling bipolar I or II disorder. There was no significant difference between the lamotrigine and the placebo treatment groups in time to need additional medications for recurrent mood symptoms.

The primary side-effect concern for lamotrigine is emergence of a rash that can, in rare cases, be life-threatening (e.g., Stevens-Johnson syndrome). A review by Bloom and Amber (2017) of lamotrigine treatment of epilepsy and bipolar disorder concluded that 8.3% of 18,698 study participants from 122 studies developed a rash, with 0.04% developing Stevens-Johnson syndrome. These findings are consistent with those from a retrospective analysis of the nearly 1,200 individuals who received lamotrigine in the bipolar disorder trials mentioned in the previous paragraph, which found that 8.3% developed a benign rash (Calabrese *et al.* 2002). Among the

1,955 individuals receiving lamotrigine in open-label settings, 0.1% developed a rash requiring hospitalization (Calabrese *et al.* 2002). Notably, 6.4% of the 1,056 individuals receiving placebo in these studies also developed a rash.

As mentioned, no other antiepileptic is FDA approved for relapse prevention in bipolar disorder. The only large double-blind randomized, placebo-controlled maintenance study of *divalproex* in bipolar I disorder found no significant difference in time to new mood episodes among divalproex, lithium, and placebo (Bowden *et al.* 2000). The study had a number of design concerns that limited interpretation, however (Keck and McElroy 2017). In other controlled studies, Tohen *et al.* (2003b) found divalproex and olanzapine to exhibit comparable relapse prevention efficacy over 47 weeks, and in a 20-month study of rapid-cycling bipolar disorder, Calabrese *et al.* (2005b) found comparable rates of relapse between divalproex and lithium. However, in a 2013 Cochrane Review (Cipriani *et al.* 2013), the authors concluded that there was insufficient evidence that valproate monotherapy is superior to placebo in relapse prevention or long-term treatment efficacy in bipolar disorder. It was also unclear if the addition of valproate significantly enhanced the efficacy of lithium monotherapy for relapse prevention. No new large-scale studies have changed those conclusions.

As with lithium, serum blood concentrations are used in the management of divalproex treatment, although the therapeutic range for this medication is wide and not well defined for bipolar disorder, mainly having been extrapolated from epilepsy treatment. In the absence of positive large-scale studies of relapse prevention with divalproex, it is no surprise that the optimal maintenance valproic acid concentration in bipolar disorder is unknown. Current practice usually consists of titrating to serum concentrations of 50-125 mg/mL and, as with lithium, balancing relapse and subsyndromal symptom prevention against minimization of side effects (Hirschfeld *et al.* 2002).

Divalproex is generally well tolerated. Common side effects include somnolence, nausea, vomiting, tremor, weight gain, and cognitive slowing. Enteric-coated and extended-release formulations (the latter requiring a 20% dosage increase to be equivalent to immediate-release formulations) have better tolerability compared with valproic acid formulations. Rare serious adverse events include pancreatitis, thrombocytopenia, significant hepatic transaminase elevation, hyperammonemic encephalopathy in individuals with urea cycle disorders, and hepatic failure. Treatment with valproate appears to pose an increased risk of polycystic ovary syndrome and teratogenicity, so its use in young women is limited (Strakowski *et al.* 2020).

Carbamazepine has been used for treating bipolar disorder for more than four decades, yet large, well-designed studies supporting its efficacy for long-term maintenance therapy are limited. Although several older studies, and a few smaller more recent ones, suggested that carbamazepine may have relapse prevention efficacy, especially for mania, these studies are methodologically very limited (Dardennes *et al.* 1995; Grunze *et al.* 2021). Like lithium, carbamazepine has a relatively narrow therapeutic index, so serum levels (target range = 4-12 mg/mL) must be monitored. Complicating the management of serum levels is the fact that carbamazepine eventually accelerates its own metabolism, requiring dosage adjustments.

Common side effects of carbamazepine include diplopia, blurred vision, ataxia, somnolence, fatigue, and nausea. Less common side effects include rash, mild leukopenia and thrombocytopenia, and hyponatremia. Rare serious adverse events include agranulocytosis, aplastic anemia, hepatic failure, pancreatitis, and exfoliative dermatitis. Ultimately, carbamazepine lacks sufficient positive long-term data to offset concerns of tolerability, complex drug-drug interactions, and the need to carefully monitor serum blood levels within a narrow therapeutic range (Strakowski *et al.* 2020). It may be less well tolerated than other treatments as well (Strakowski *et al.* 2001). The related antiepileptic oxcarbazepine, although better tolerated, simply lacks sufficient data supporting a role in the treatment of bipolar disorder, and particularly long-term treatment (Grunze *et al.* 2021).

Atypical Antipsychotics

Several recent articles have described a dramatic decline in the prescription of lithium for bipolar disorder over the past two decades, with a concurrent expanded use of the so-called second-and third-generation antipsychotics (see, e.g., Rhee *et al.* 2020). These medications are generally viewed as easier to prescribe and have been widely marketed, although there is no evidence of their superiority to lithium for long-term management. Unlike the historic (typical) dopamine D_2 antagonist antipsychotics (previously known as "neuroleptics"), these later-generation medications appear, at the least, to lack depressogenic effects, and at the most, to potentially possess antidepressant effects.

Olanzapine was the first of these to gain an FDA indication for relapse prevention. Tohen *et al.* (2005) found that olanzapine was comparable to lithium for relapse prevention in a 1-year comparison trial and comparable to divalproex in a 47-week comparison trial (Tohen *et al.* 2003b). Olanzapine exhibited superiority over placebo in preventing both manic and depressive episodes over 48 weeks (Tohen *et al.* 2006), leading to FDA approval for this indication. Olanzapine combined with lithium or divalproex was superior in efficacy to placebo and to monotherapy with either lithium or divalproex for relapse prevention over 18 months in individuals who initially responded to the active combination acutely (Tohen *et al.* 2002b) and then were re-randomized (Tohen *et al.* 2004). However, the olanzapine-treated group exhibited twice the weight gain of the monotherapy groups, and weight gain and associated metabolic syndrome are problematic with long-term olanzapine therapy in general. Recently, the combination drug (Lybalvi) of olanzapine 5-20 mg plus samidorphan 10 mg was also approved for the maintenance treatment of bipolar disorder (Citrome *et al.* 2021). Samidorphan is a m opioid antagonist. The combination appears to have less weight gain liability than olanzapine monotherapy.

The partial dopamine D_2 antagonist, and so-called third-generation antipsychotic, *aripiprazole* is also FDA approved for maintenance therapy as oral and long-acting injectable formulations. This approval arose from studies in which aripiprazole was superior to placebo in preventing manic relapse over a 6-month follow-up period in individuals with bipolar disorder initially stabilized on aripiprazole monotherapy for an acute manic or mixed episode (Keck *et al.* 2006, 2007). Of note, however, for depressive relapse, aripiprazole did not exhibit a significant difference from placebo. In a 52-week study, the long-acting injectable formulation (Maintena) was superior to placebo injection in increasing time to recurrence of any mood episode and in percentage of patients experiencing a recurrence of any mood episode (Calabrese *et al.* 2017). Aripiprazole is generally well tolerated, although it commonly causes gastrointestinal distress at drug initiation (often requiring a low-dose start with titration over time) and akathisia. Aripiprazole has also been shown to be effective for maintenance treatment as adjunctive treatment with lithium or divalproex (Vieta *et al.* 2010b).

Asenapine has controlled clinical trial evidence supporting FDA approval for monotherapy maintenance treatment of bipolar disorder, suggesting that it may be a useful compound for relapse prevention, although, again, like most other antipsychotics, its effects are perhaps stronger for mania than for depression prevention (McIntyre *et al.* 2010; Szegedi *et al.* 2018). Asenapine can be sedating and may have a higher risk for extrapyramidal side effects (EPS) than other second-and third-generation antipsychotics (Vieta and Montes 2018).

In two randomized controlled trials, the long-acting injectable formulation of *risperidone* was superior in efficacy to placebo in prevention of relapse, both as monotherapy and as adjunctive therapy (Quiroz *et al.* 2010; Vieta *et al.* 2012), and is FDA approved for this indication. Risperidone produces some sedation and has a relatively high risk for EPS, particularly at dosages of 6 mg/day or higher (Hirschfeld *et al.* 2004; Khanna *et al.* 2005; Yatham *et al.* 2003).

It also elevates prolactin more than do other second-generation antipsychotics, although the clinical impact of the laboratory measure is not clear. Similarly, the risperidone metabolite paliperidone, in the extended-release formulation, may also be efficacious as a maintenance treatment in bipolar disorder (Berwaerts *et al.* 2012a), although it is much less studied.

Quetiapine and *ziprasidone* in combination with lithium or divalproex have both been demonstrated to potentially increase time to relapse or intervention in bipolar disorder compared with lithium or divalproex monotherapy (Bowden *et al.* 2010; Suppes *et al.* 2009; Vieta *et al.* 2008). Consequently, both are FDA approved for combination maintenance therapy, although neither is approved for maintenance monotherapy. There is some evidence that quetiapine may have long-term treatment efficacy in relapse prevention of mania and depression (Miura *et al.* 2014). It is generally well tolerated, although it is frequently sedating and is associated with weight gain and metabolic syndrome. Ziprasidone has limited evidence for acute antidepressant efficacy or usefulness in preventing depression relapse as monotherapy. Although less likely to be associated with weight gain, ziprasidone has cardiovascular effects that have to be managed.

Neuromodulatory Therapies

Recent interest in neuromodulatory therapies in psychiatry has continued to increase, although the utility of these technologies for bipolar disorder maintenance treatment is not adequately studied. The oldest of these, electroconvulsive therapy (ECT), is clinically used at times in the maintenance treatment of bipolar disorder but has never been systematically studied in a randomized controlled trial. Several naturalistic studies suggest that maintenance ECT may be a useful treatment alternative for patients whose symptoms are inadequately responsive to pharmacotherapy (Keck and McElroy 2017; Schwarz *et al.* 1995; Vanelle *et al.* 1994). ECT is relatively well tolerated, although it is associated with memory loss, especially with bilateral stimulation. In more recent research, repetitive transcranial magnetic stimulation (rTMS) is being investigated for use in bipolar disorder. However, there are no adequate controlled relapse prevention studies to date to allow determination of the role of rTMS in long-term maintenance treatment of bipolar disorder (Gold *et al.* 2019).

Psychotherapy

Although pharmacotherapy is necessary and critical in the management of bipolar disorder, alone it is rarely sufficient. Bipolar disorder creates significant psychosocial disruption, and, generally, the addition of an evidence-based psychotherapy appears beneficial (Geddes and Miklowitz 2013; Yatham *et al.* 2018). Consequently, for maintenance treatment, the combination of therapy and medications is recommended. Several specific adjunctive psychosocial interventions have been demonstrated to improve long-term outcomes in bipolar disorder (reviewed in O'Donnell and Miklowitz 2020). The best-studied of these include group psychoeducation, interpersonal and social rhythm therapy (IPSRT), family-focused therapies (FFTs), cognitive-behavioral therapies (CBTs), and, more recently, mindfulness-based CBT approaches (O'Donnell and Miklowitz 2020; Xuan *et al.* 2020). Several of these have been examined in large randomized controlled trials conducted over 1-to 2-year follow-up periods. In general, studies suggest that these psychotherapy modalities tend to increase treatment adherence, reduce or delay mood episode recurrence (particularly depression), and improve function when used adjunctively with medications (as compared with use of medications alone). Specifically, efficacy for improved longer-term outcomes has been shown relatively consistently with IPSRT (Frank *et al.* 2005; Swartz *et al.* 2018), FFT (Kim and Miklowitz 2004; Miklowitz *et al.* 2003), and group psychoeducation (Colom *et al.* 2003, 2009), but less consistently with CBT (Jones *et al.* 2015; Lam *et al.* 2005; Scott *et al.* 2006), including mindfulness-based CBT (Xuan *et al.* 2020).

Treatment of Manic and Mixed Episodes

Mania is often a medical emergency and frequently requires inpatient care to ensure the affected individual's safety, to initiate treatment, and to support family members. Mixed episodes comprise both depressive and manic symptoms and may increase the risk of suicide as well as other negative outcomes. With these risks in mind, the primary goal of treatment of manic and mixed episodes is establishing a safe treatment environment, followed by rapid symptom reduction, leading to symptom remission and recovery and restoration of psychosocial and vocational functioning (Hirschfeld *et al.* 2002).

Perhaps because it is dramatic and potentially life-threatening, and because mania fortunately responds to antidopaminergic treatments (i.e., antipsychotics), the treatment of mania is the most extensively studied phase of bipolar illness. Consequently, a number of FDA-approved treatment options are available (Table 49-1). Moreover, individuals in mixed states were often included in the FDA registration trials, so that the same treatments apply to these more complex cases; in fact, there are no FDA-approved treatments for mixed states only. Finally, the treatment of hypomania is little studied, in part because individuals with hypomania rarely seek care. Consequently, our discussion of treatment of mania, at this time, also applies to the treatment of mixed episodes and hypomania, so the latter will generally not be discussed further.

TABLE 49-1. Commonly used pharmacological treatments in bipolar disorder, by phase of illness

Medication	Mania	Depression	Maintenance
Lithium	X, Y	A	X, Y
Antiepileptics			
Divalproex	X	B	B
Carbamazepine	X	C	B
Lamotrigine	D	A	X
Atypical antipsychotics			
Risperidone	X, Y	C	X[1]
Olanzapine	X, Y	X[2]/B[3], Y	X[4]
Ziprasidone	X	D	X[5]
Quetiapine	X, Y	X	X[5]
Aripiprazole	X, Y	D[6]	X

Medication	**Mania**	**Depression**	**Maintenance**
Lurasidone	C	X, Y	C
Asenapine	X, Y	C	X
Paliperidone	A	D	B
Clozapine	C	D	C
Cariprazine	X	X	D
Brexpiprazole	C	D	D
Conventional antipsychotics			
Chlorpromazine	X	D	D
Haloperidol	A	D	D

Note: X = FDA approved for this phase; if not FDA approved, then: A = replicated double-blind placebo-controlled clinical trial or meta-analysis demonstrating efficacy; B = at least one double-blind placebo controlled trial demonstrating efficacy; C = uncontrolled trials or expert clinical use/opinion; D = minimal evidence for efficacy or failed trials.

Y = FDA approved for bipolar disorder in youth (typically ages 10-17 years).

[1] FDA approved in slow-release injectable form.

[2] FDA approved in combination with fluoxetine.

[3] As monotherapy.

[4] Also FDA approved in combination with samidorphan.

[5] FDA approved for augmentation of lithium or divalproex.

[6] FDA approved for augmentation therapy in major depressive disorder, not bipolar depression.

Source. Adapted from Strakowski SM, Almeida J, DelBello MP: "Psychopharmacological treatments for bipolar disorder," in *Primer on Bipolar Disorder*. Edited by Strakowski SM, Fleck DE, Adler CM, DelBello MP. New York, Oxford University Press, 2020, pp 189-228.

Pharmacotherapy is the cornerstone of treatment of acute manic and mixed episodes, and in contrast to maintenance treatment, psychotherapies beyond supportive therapy have a limited role, at least during the acute phase. Overall, the widely used and FDA-approved treatments for mania typically lead to improvement in 50%-60% of individuals in 3-4 weeks. However, monotherapy is rarely effective for full recovery and long-term stability, as noted in the last section, and at times combination therapy is necessary to even achieve remission of the acute manic episode (Suppes *et al.* 2005).

Lithium

Lithium was discovered in 1946, largely through an insightful accident, by John Cade, and it revolutionized the care of people with bipolar disorder specifically and how we approach psychiatric illnesses more generally. Following a series of studies in the 1950s, lithium quickly became the mainstay of treatment for acute mania and has remained so for more than 60 years; its superiority to placebo is definitively established (as reviewed in Goodwin and Jamison 2007), and its efficacy has been shown to be equivalent to that of divalproex (Bowden *et al.* 1994), carbamazepine (Lerer *et al.* 1987; Small *et al.* 1991), risperidone (Segal *et al.* 1998), olanzapine (Berk *et al.* 1999), quetiapine (Bowden *et al.* 2005), aripiprazole (Keck *et al.* 2003a), and typical antipsychotics (Garfinkel *et al.* 1980; Johnson *et al.* 1971; Platman 1970; Prien *et al.* 1972; Shopsin *et al.* 1975; Spring *et al.* 1970; Takahashi *et al.* 1975). Importantly, lithium produced improvement in psychotic, as well as manic, symptoms in these trials; consequently, it is the only known medication that treats psychosis in only a single condition (as opposed to the antipsychotics, which work more broadly). Finally, lithium appears to also uniquely decrease the risk of suicide in bipolar disorder (Lewitzka *et al.* 2015). As noted previously, lithium use has dramatically declined in the past 10-20 years; given its unique properties, it is unlikely that this decline is ultimately in the best interest of people with bipolar disorder.

In the treatment of acute mania, lithium response is maximized by titrating to plasma concentrations at the upper end of the therapeutic range (1.0-1.4 mmol/L) as tolerated (Stokes *et al.* 1976). In randomized controlled trials, responders typically demonstrate significant clinical improvement within 1-2 weeks, although full remission often requires additional time (Keck and McElroy 2001).

Antiepileptics

Divalproex and related formulations of valproic acid exhibited superior efficacy in randomized controlled treatment trials of acute bipolar manic or mixed episodes when compared with placebo (Bowden *et al.* 1994, 2006; Brennan *et al.* 1984; Emrich *et al.* 1981; Pope *et al.* 1991), and showed equivalent efficacy to lithium (Bowden *et al.* 1994; Freeman *et al.* 1992), haloperidol (McElroy *et al.* 1996), and olanzapine (Zajecka *et al.* 2002). However, divalproex was inferior to olanzapine in mean reduction of manic symptoms and proportion of individuals achieving remission in a second comparison trial (Tohen *et al.* 2002a). Muller-Oerlinghausen *et al.* (2000) found that valproate augmentation of typical antipsychotics permitted significantly lower mean antipsychotic doses while yielding higher response rates compared with placebo augmentation in the treatment of acute mania.

Acute antimanic response is associated with divalproex plasma concentrations between 50 and 125 mg/L, with some evidence of greater response at the upper end of the therapeutic range (Allen *et al.* 2006; Zajecka *et al.* 2002). However, these dosage ranges were largely extrapolated from epilepsy studies, and specific antimanic dose-finding studies are limited. Consequently, some individuals require dosing outside this range, although side effects become progressively more problematic with plasma concentrations above 125 mg/L. Divalproex initiated at a dosage of 20-30 mg/kg/day has shown good tolerability, and perhaps a more rapid response, than gradual titration from a lower (e.g., 750 mg/day) starting dosage (Hirschfeld *et al.* 1999; Keck *et al.* 1993). This "loading dose" strategy, then, is recommended.

Carbamazepine, as an extended-release formulation, was superior in efficacy to placebo in two large randomized, placebo-controlled multicenter trials (Weisler *et al.* 2004b, 2005). These findings replicated earlier results from a placebo-controlled crossover trial (Ballenger and Post 1978). As noted previously, the complex side-effect profile and the pharmacokinetic and pharmacodynamic properties of carbamazepine often limit its use in the treatment of acute mania and bipolar disorder more generally.

In the only large randomized, placebo-controlled multicenter trial of *oxcarbazepine* in acute mania to date, a 7-week study in children and adolescents, oxcarbazepine was not superior to placebo in terms of reduction of manic symptoms (Wagner *et al.* 2006). Although sometimes used because of its putative similarities in mechanism of action to carbamazepine, while being better tolerated, the use of oxcarbazepine in acute bipolar mania is not supported by evidence from clinical studies.

Antipsychotics

Conventional (First-Generation) Antipsychotics

Chlorpromazine (Klein 1967) and haloperidol (McIntyre *et al.* 2005) were found to be superior in efficacy to placebo in randomized controlled trials of acute mania treatment. Chlorpromazine was first identified as an antipsychotic in a cohort of individuals

with what was in all likelihood psychotic mania but ended up instead being developed primarily for the treatment of schizophrenia, which it revolutionized (Ban 2007). It is FDA approved for the treatment of acute mania, nonetheless. Typical antipsychotics bear the burden of neurological and neuroendocrinological side effects and may carry an increased risk of postmanic depressive episodes (Kukopulos *et al.* 1980). Consequently, although clearly effective in the treatment of acute mania, these medications are not recommended in general for long-term treatment.

Second-and Third-Generation Antipsychotics

The second-and third-generation antipsychotics have become the primary medications used in the treatment of acute mania specifically and in bipolar disorder more generally. All are D_2 receptor antagonists, and this mechanism likely underlies their antimanic properties. These agents are also effective primary treatments for psychotic disorders more generally (e.g., schizophrenia). The atypical antipsychotics olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine, and cariprazine have all shown efficacy in the treatment of acute bipolar mania in at least two randomized, placebo-controlled trials. They are all FDA approved for this indication.

Olanzapine was found to be superior in efficacy to placebo (Tohen *et al.* 1999, 2000), superior or equal in efficacy to divalproex (Tohen *et al.* 2002a; Zajecka *et al.* 2002), and comparable in efficacy to lithium (Berk *et al.* 1999; Niufan *et al.* 2008), risperidone (Perlis *et al.* 2006), and haloperidol (Tohen *et al.* 2003a) in mean reduction of manic and mixed symptoms in 3- to 4-week monotherapy trials. Adjunctive treatment with olanzapine was superior in efficacy to placebo in individuals whose symptoms were inadequately responsive to lithium or divalproex (Tohen *et al.* 2002b). The most common side effects associated with olanzapine were somnolence, constipation, dry mouth, increased appetite, weight gain, and orthostatic hypotension.

Risperidone was superior to placebo (Hirschfeld *et al.* 2004; Khanna *et al.* 2005) and comparable in efficacy to olanzapine (Perlis *et al.* 2006), haloperidol (Smulevich *et al.* 2005), and lithium (Segal *et al.* 1998) in mean reduction of manic and mixed symptoms as monotherapy in 3-to 4-week trials. Risperidone was superior in efficacy to placebo as an adjunctive therapy with lithium or divalproex in one controlled trial (Sachs *et al.* 2002), but not in a second (Yatham *et al.* 2003). The rate of EPS associated with risperidone was low when the drug was administered at average dosages up to 4 mg/day (Hirschfeld *et al.* 2004; Sachs *et al.* 2002; Yatham *et al.* 2003), but not when administered at an average dosage of 6 mg/day or greater (Hirschfeld *et al.* 2004; Khanna *et al.* 2005; Yatham *et al.* 2003). Other commonly occurring side effects included prolactin elevation, akathisia, somnolence, dyspepsia, and nausea. Placebo-controlled trials of the extended-release formulation of the atypical antipsychotic *paliperidone* (a risperidone metabolite) in acute mania yielded mixed findings (Berwaerts *et al.* 2011, 2012b; Vieta *et al.* 2010a), and a recent meta-analysis concluded that it does not offer significant benefits over placebo (Chang *et al.* 2017).

Quetiapine was superior in efficacy to placebo as monotherapy for acute mania in two 12-week studies in adults (Bowden *et al.* 2005; McIntyre *et al.*

2005) and was comparable in efficacy to lithium in a 4-week study in adults (Li *et al.* 2008). Similarly, quetiapine was superior in efficacy to placebo as an adjunctive treatment with lithium or divalproex (Sachs *et al.* 2004; Yatham *et al.* 2004). The mean modal dosage of quetiapine associated with antimanic efficacy in most studies was approximately 600 mg/day (Vieta *et al.* 2005b). Quetiapine was also superior to placebo in the reduction of hypomanic or mild manic symptoms among outpatients in an 8-week trial (McElroy *et al.* 2010a).

Ziprasidone was superior in efficacy to placebo (mean dosage = 120-130 mg/day) in two 3-week monotherapy trials in adults with acute mania (Keck *et al.* 2003b; Potkin *et al.* 2005) and comparable in efficacy to haloperidol in a 12-week trial (Ramey *et al.* 2003). Ziprasidone was not superior to placebo as an adjunctive treatment with lithium in a study designed to prove superior onset of action by 2 weeks of treatment (Weisler *et al.* 2004a). *Asenapine* was superior to placebo in mean reduction of manic symptoms in two 3-week trials (McIntyre *et al.* 2009, 2010).

Among the third-generation antipsychotics, *aripiprazole* had significantly greater efficacy in the reduction of manic symptoms compared with placebo in three 3-week trials (Keck *et al.* 2003a, 2007; Sachs *et al.* 2006), and equivalent efficacy compared with haloperidol (Vieta *et al.* 2005a) and lithium (Keck *et al.* 2009) in 12-week comparison trials. Aripiprazole was initiated at 15 or 30 mg/day. *Cariprazine*, a dopamine D_3 and D_2 receptor partial agonist, was superior to placebo in reduction of manic symptoms in three randomized controlled trials (Calabrese *et al.* 2015; Durgam *et al.* 2015; Sachs *et al.* 2015). The most common side effects associated with cariprazine (occurring in more than 10% of subjects and at twice the rate found with placebo) were akathisia, EPS, tremor, dyspepsia, and vomiting.

In general, there are no studies suggesting that any one atypical antipsychotic is more effective than any other in the treatment of acute mania. Side-effect profiles differ, and this may influence choice. As previously reviewed, there are differences in long-term relapse prevention data that may also guide choices for treating mania; namely, it may be prudent to start in the acute phase with a drug that will be used long term. Moreover, in the studies of atypical antipsychotics reviewed, no significant differences in response were seen between individuals with and without psychotic features or between those with manic episodes and those with mixed episodes, except in trials of quetiapine, many of which excluded patients with mixed episodes. The prototypical atypical agent clozapine was reported to have substantial efficacy in several large case series of individuals with treatment-refractory mania (Calabrese *et al.* 1996; Green *et al.* 2000), but clozapine has not been studied in placebo-controlled studies in mania.

Neuromodulatory Therapies

Electroconvulsive therapy is an important and underutilized treatment option for severe mania, particularly with marked psychotic or catatonic symptoms. ECT was superior in efficacy both to lithium (Small *et al.* 1988) and to the combination of lithium and haloperidol (Mukherjee *et al.* 1994) in prospective comparison studies. In addition, ECT in combination with chlorpromazine was superior to sham ECT and chlorpromazine (Sikdar *et al.* 1994). Although these studies were small, their findings are consistent with those of other naturalistic studies of ECT in the treatment of acute mania (Black *et al.* 1987; Thomas and Reddy 1982) as well as clinical practice. There is a risk of neurotoxicity in individuals receiving ECT while receiving lithium; consequently, lithium should be discontinued when ECT is administered (Hirschfeld *et al.* 2002). Other neuromodulatory therapies (e.g., rTMS) have not been studied sufficiently to recommend use during mania.

Treatment of Acute Depressive Episodes

Although bipolar disorder is defined by the occurrence of mania, depressive symptoms dominant the "ill time" of the condition (Judd *et al.* 2002). The goal of treatment of bipolar depression is full remission of symptoms, including preventing suicide (Hirschfeld *et al.* 2002). This straightforward goal is complicated by the limited efficacy of many mood stabilizers (Zornberg and Pope 1993) and antidepressants in the treatment of bipolar disorder (Sachs *et al.* 2007). Ultimately, as suggested earlier, the optimal approach is to aggressively manage the diagnosis by maximizing compounds effective for long-term relapse prevention.

Lithium

Eight of nine placebo-controlled trials conducted in the 1960s and 1970s in people with bipolar I and II disorders found lithium superior in efficacy to placebo in acute bipolar depression (reviewed in Zornberg and Pope 1993). In an analysis of five studies in which it was possible to distinguish "unequivocal" lithium responders from those with partial but incomplete improvement in depression, Zornberg and Pope (1993) reported that 36% had an unequivocal response, compared with 79% who had partial but incomplete benefit.

Second-and Third-Generation Antipsychotics

Quetiapine (300 mg/day and 600 mg/day) is FDA approved for the treatment of bipolar depression; it was superior to placebo in reducing depressive symptoms in four large 8-week multicenter trials involving individuals with bipolar I and II depression (Calabrese *et al.* 2005a; McElroy *et al.* 2010b; Thase *et al.* 2006; Young *et al.* 2010). Although both dosages similarly improved symptoms, the rate of side effects was lower in the 300 mg/day groups compared with the 600 mg/day groups. New episodes of mania were few and similar across all treatment groups, including placebo.

Both *olanzapine* and the *olanzapine-fluoxetine* combination (OFC) were superior to placebo in reducing depressive symptoms in an 8-week trial with depressed bipolar I disorder patients (Tohen *et al.* 2003c). However, the combination treatment was superior to placebo throughout the trial, and was superior to olanzapine monotherapy from week 4 onward; consequently, OFC received FDA approval for this indication. No significant differences in new cases of mania were observed between patients with and without the addition of fluoxetine. Brown *et al.* (2006) compared OFC with lamotrigine (titrated to 200 mg/day) in a 7-week comparison trial in depressed bipolar I disorder patients and observed greater reductions in depressive symptoms in the OFC group. However, the necessary slow titration of lamotrigine makes interpretation difficult (i.e., lamotrigine was underdosed for a significant portion of the study). New cases of mania were not significantly different between the two groups.

Lurasidone was more effective than placebo for the treatment of depressed bipolar I disorder patients in two large FDA registration trials (reviewed by Franklin *et al.* 2015). Notably, the onset of therapeutic effect occurred within the first 2-3 weeks of treatment among responders. Lurasidone is significantly less likely than other atypical agents to produce metabolic side effects, although it is associated with sedation, akathisia, and gastrointestinal side effects.

Cariprazine is a dopamine D_2 and D_3 receptor partial antagonist that is FDA approved for the treatment of depression in bipolar I disorder (reviewed in a meta-analysis by Pinto *et al.* [2020]). It has a relatively high risk for akathisia and gastrointestinal distress but is generally well tolerated and has a low risk of weight gain.

Antiepileptics

Lamotrigine is FDA approved for the prevention of depressive episodes, but not for the treatment of acute depression. In an initial large 7-week randomized, placebo-controlled trial, lamotrigine (at 50 mg/day and 200 mg/day) was superior to placebo in depressed bipolar I disorder patients (Calabrese *et al.* 1999), with no differences among groups in new manic episodes. A second large placebo-controlled, parallel-group, flexible-dose trial involving depression in both bipolar I and II disorder did not find a significant advantage for lamotrigine over placebo, however (Bowden 2001). In a double-blind crossover trial, Frye *et al.* (2000) found lamotrigine superior to placebo in improving depression in individuals with treatment-refractory rapid-cycling bipolar I or II disorder. Lamotrigine was superior to placebo when added to lithium treatment in an 8-week trial in individuals with bipolar disorder and breakthrough depressive episodes (van der Loos *et al.* 2009).

Divalproex has been relatively understudied and has mixed results in bipolar depression. For example, Sachs and Collins (2001) did not find divalproex to be superior in efficacy to placebo in a pilot trial, whereas Davis *et al.* (2005) found divalproex superior to placebo in reduction of depressive and anxiety symptoms in a later pilot study. Bond *et al.* (2010) completed a meta-analysis of available data and concluded that the relative likelihood of response to divalproex was greater than that to placebo (RR = 1.6-2.1). These authors interpreted the results to suggest "preliminary evidence" for efficacy of divalproex for the treatment of bipolar depression.

Carbamazepine has limited data supporting its efficacy in bipolar depression. In two small controlled trials in treatment-refractory bipolar depression, response to carbamazepine was superior to that seen with placebo (Post *et al.* 1986) or lithium (Small 1990). The results of these initial intriguing findings from small studies have not been followed by large placebo-controlled, parallel-group studies. In part, as discussed, the complexities of managing carbamazepine therapy may limit enthusiasm for larger studies.

Antidepressants

The evidence base for the efficacy of standard antidepressant medications for the treatment of depression in bipolar disorder is meager. Recent studies and meta-analyses (e.g., Cheniaux and Nardi 2019; Sachs *et al.* 2007; Sidor and MacQueen 2012) suggest a limited role for these medications in bipolar I disorder. However, antidepressants may have a larger role in depression in bipolar II disorder (Amsterdam and Shults 2005). Notably, switch rates associated with newer antidepressants in short-term studies, in general, appear to be lower than those associated with tricyclic antidepressants (TCAs) in older studies (Thase and Sachs 2000), although efficacy appears no better. Among all of the antidepressants studied, the most substantial evidence for efficacy rests with the monoamine oxidase inhibitor (MAOI) tranylcypromine (Himmelhoch *et al.* 1991), but safety concerns often eliminate this agent from first-line therapy choices (Hirschfeld *et al.* 2002).

Bupropion (Sachs *et al.* 1994) and selective serotonin reuptake inhibitors (SSRIs) (Nemeroff *et al.* 2001) are commonly administered in conjunction with mood stabilizers, so they may have a secondary role in some individuals. At this point in time, the cumulative evidence suggests that antidepressants are at most an adjunctive treatment choice in bipolar depression, even when delivered as a combination drug (i.e., OFC, with fluoxetine considered as an adjunct in this case) (Strakowski *et al.* 2020). Whether there are subtypes of bipolar disorder or subgroups of patients in which antidepressants may play a more prominent role remains to be defined.

Neuromodulatory Therapies

Electroconvulsive therapy is perhaps the most effective antidepressant available, including in the treatment of depressed individuals with bipolar disorder. ECT had significantly greater efficacy than MAOIs, TCAs, or placebo in several randomized controlled trials in patients with bipolar depression (reviewed in Zornberg and Pope 1993). ECT may be particularly indicated for individuals with severe, psychotic, or catatonic symptoms.

Repetitive transcranial magnetic stimulation is FDA approved for treatment of "treatment-resistant depression," but its role in bipolar depression remains undefined. To date, study results are mixed regarding efficacy, and rTMS may be associated with manic switch in some individuals (Gold *et al.* 2019).

Ketamine

Ketamine is an FDA approved anesthetic that has been recently used, in subanesthetic doses, to rapidly improve symptoms, including suicidality, in unipolar and bipolar depression (Grady *et al.* 2018; McIntyre *et al.* 2020). In a nasal administration form, it is FDA approved for treatment-resistant depression in adults, as an adjunct to standard antidepressant therapy. Its role in bipolar disorder remains to be defined.

Psychotherapy

Very few randomized controlled trials of any form of psychotherapy have been conducted for acute bipolar depression (O'Donnell and Miklowitz 2020). Swartz *et al.* (2018) compared IPSRT plus placebo versus IPSRT plus quetiapine in acutely depressed adults with bipolar II disorder. The IPSRT plus quetiapine group improved faster. CBT and interpersonal therapy have demonstrated efficacy in the treatment of unipolar major depressive disorder, but these modalities have been examined only in very small preliminary studies in patients with bipolar depression, thus far without conclusive findings (Cole *et al.* 2002; O'Donnell and Miklowitz 2020; Zaretsky *et al.* 1999). The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) included a 2-year randomized trial of three intensive psychotherapies--namely, IPSRT, CBT, and FFT. Recovery rates did not differ among therapies, but individuals receiving therapies in conjunction with medication treatment exhibited better recovery from the index depression (Miklowitz *et al.* 2007).

Conclusion

During the past two decades, there has been a steady increase in available treatments for bipolar disorder, although the bulk of studies have been for the treatment of acute

mania. Consequently, a number of medications have demonstrated efficacy in the treatment of acute mania in placebo-controlled trials, either as monotherapy or as an adjunct to mood stabilizers. In addition, evidence suggests that combination therapy with an antipsychotic and another class of mood stabilizer (e.g., lithium) is more rapidly effective, with better overall response rates in acute mania, than either treatment alone. However, whether this effect is "absolute" or simply faster is not known.

In contrast, the treatment of bipolar depression remains one of the least-studied aspects of modern psychiatry, particularly given the prevalence, morbidity, and mortality associated with this condition. Complicating this gap in treatment knowledge, it has become increasingly clear that antidepressants provide only limited efficacy in bipolar disorder, and therefore are suboptimal interventions. Long-term relapse prevention--so-called maintenance therapy--is also understudied; even though a few compounds have received FDA approval for this purpose, lithium remains the best-studied choice.

As noted at the beginning of this chapter, perhaps the most parsimonious approach to managing bipolar disorder is to optimize treatments with proven efficacy, especially efficacy for maintenance therapy. With this approach in mind, combinations of these medications are perhaps the current best practice; as noted in this chapter and elsewhere, however, polypharmacy exceeding three daily medications is generally not recommended. Instead, a careful trial-and-error process to identify the best two-or three-medication combination plus an evidence-based therapy that optimizes function and the amount of time spent in a euthymic state is the best approach. This approach requires careful documentation, a lot of psychoeducation, and a coordinated treatment team (Strakowski *et al.* 2020). Nonetheless, despite a number of persisting gaps in treatment knowledge, the options available for people with bipolar disorder have dramatically expanded, suggesting that better treatments are just over the horizon.

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CHAPTER 50

Treatment of Anxiety Disorders

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Anxiety disorders are one of the most common psychiatric disorders, with a lifetime prevalence of more than 20% (Kessler *et al.* 2005a). The course of anxiety disorders varies. Some patients have transient and subsyndromal symptoms that do not require treatment, whereas others experience significant distress with a chronic and fluctuating course of illness. In this chapter, we review the main findings from double-blind and some open-label trials of psychopharmacological treatment for anxiety disorders.

Panic Disorder

Panic disorder severity and treatment outcomes can be measured with the clinician-or self-rated Panic Disorder Severity Scale (Shear *et al.* 1997). Other widely used measures include the Sheehan Panic and Anticipatory Anxiety Scale (Sheehan 1986) and the self-rated Marks-Mathews Fear Questionnaire (Marks and Mathews 1979). The desired endpoint is full remission, although this is not always attainable. Effective treatment results in reduced emergency department and laboratory resource use (Roy-Byrne *et al.* 2001).

First-Line Pharmacotherapy

Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors

In a meta-analysis, Boyer (1995) reported that selective serotonin reuptake inhibitors (SSRIs) were more effective than imipramine and alprazolam in treating panic disorder. However, a meta-analysis by Otto *et al.* (2001) failed to confirm these findings. Evidence is now available in support of the SSRIs citalopram (Wade *et al.* 1997), escitalopram (Stahl *et al.* 2003), fluoxetine (Michelson *et al.* 1998, 2001), fluvoxamine (Asnis *et al.* 2001; Black *et al.* 1993), paroxetine (Ballenger *et al.* 1998; Oehrberg *et al.* 1995; Sheehan *et al.* 2005), and sertraline (Londborg *et al.* 1998) as well as the nonselective serotonin reuptake inhibitor clomipramine (Lecrubier *et al.* 1997a). Fluoxetine, paroxetine, and sertraline are FDA approved for the treatment of panic disorder.

The extended-release formulation of venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), demonstrated greater efficacy than placebo for patients with panic disorder in a 10-week trial (Bradwejn *et al.* 2005). In addition, extended-release venlafaxine was as effective as paroxetine in a 12-week placebo-controlled trial (Pollack *et al.* 2007) and is FDA approved for the treatment of panic disorder. Extended-release venlafaxine is well tolerated, with an adverse-effect profile comparable to that observed when it is used to treat depressive and other anxiety disorders. Although no systematic data are currently available supporting the use of other SNRIs in the treatment of panic disorder, duloxetine and milnacipran significantly alleviated panic disorder symptoms in open trials (Blaya *et al.* 2007; Simon *et al.* 2009).

Patients with panic disorder are often extremely sensitive to the activating effects of antidepressants. They have poor tolerance of symptoms such as palpitations, sweating, and tremor and frequently discontinue treatment or drop out. This problem can almost always be prevented by coprescribing a benzodiazepine (Goddard *et al.* 2001; Pollack *et al.* 2003) or by starting with a low dosage of an SSRI and increasing it gradually as tolerated. The recommended starting dosages of antidepressants for panic disorder are approximately half those given for depressive disorders

(American Psychiatric Association 2010), but dosages should be gradually increased to dosages similar to those used to treat depressive disorders. Because average dosages used to treat anxiety disorders are as high as (or higher than) those used to treat depressive disorders, both physician availability and thorough patient preparation and education are crucial for promptly addressing any uncomfortable side effects. Other common side effects of SSRIs include weight gain, sexual dysfunction, sleep impairment, and potential drug-drug interactions.

Within SSRIs, it is considered that the efficacy is comparable. If a response is not elicited from an SSRI, the subsequent step would entail attempting an alternative SSRI or switching to an SNRI.

Treatment discontinuation can lead to relapse, which mimics panic symptoms and is quite distressing. Gradual dosage reduction is recommended, as are patient education, physician availability, and coping strategies such as cognitive-behavioral therapy (CBT) (Otto *et al.* 1993). Switching to a long-acting SSRI such as fluoxetine may be considered. Serotonin 5-HT_2 or 5-HT_3 receptor antagonists (e.g., mirtazapine, ondansetron) may be used to limit some of the symptoms mediated through these pathways (e.g., insomnia, agitation, gastrointestinal distress).

Other Pharmacological Approaches

Benzodiazepines

The Cross-National Collaborative Panic Study (1992) showed that alprazolam, along with imipramine, was more effective for panic disorder than placebo. Lydiard *et al.* (1992) reported that alprazolam 2 mg/day was more effective than placebo. Efficacy for clonazepam in panic disorder was also demonstrated (Davidson and Moroz 1998; Rosenbaum *et al.* 1997; Tesar *et al.* 1991). Alprazolam and clonazepam are FDA approved for the treatment of panic disorder. Although the evidence was judged to be of low quality, previous Cochrane Reviews reported the superiority of benzodiazepines over placebo in the short-term treatment of panic disorder (Breilmann *et al.* 2019) and comparable efficacy of benzodiazepines and antidepressants for panic symptoms (Bighelli *et al.* 2016). Benzodiazepines are widely prescribed for the treatment of panic disorder, primarily because of their rapid onset of action. However, because of the risks of dependency and withdrawal symptoms, it is suggested that benzodiazepines should be avoided as first-line treatment or should generally only be used for a limited time (American Psychiatric Association 2010; Baldwin *et al.* 2014).

Alprazolam (and other benzodiazepines) are now regarded as a second-line treatment for panic disorder. Problems include sedation at higher dosages, abuse liability, and discontinuation-related distress. Clonazepam has an advantage over alprazolam because of its longer half-life; however, clonazepam can also result in sedation, depression, and discontinuation symptoms. One review has supported a role for clonazepam alone or in combination with SSRIs and/or CBT in the management of panic disorder (Nardi *et al.* 2013).

The use of benzodiazepines is a particular concern for elderly patients. Many elderly individuals are more prone to sedation and falls, which can result in fractures and potential head injury; they are also more likely to experience discontinuation problems.

Tricyclic Antidepressants

Although tricyclic antidepressants (TCAs) are effective (for a review, see Freire *et al.* 2014; Sartori and Singewald 2019), they are considered second-line treatments for panic disorder because of their side effects. Imipramine is the most well studied of the TCAs in panic disorder. Mavissakalian and Perel (1995) found that phobic symptoms responded best if the plasma level of imipramine and desmethylimipramine ranged from 110 to 140 ng/mL, whereas control of panic attacks tended to occur at lower plasma levels. As with SSRIs and SNRIs, low starting dosages in the range of 10-25 mg/day are in order, with gradual titration thereafter per patient tolerance until response is achieved.

Monoamine Oxidase Inhibitors

Sheehan *et al.* (1980) found that phenelzine, along with imipramine, was more effective than placebo in the treatment of panic disorder with agoraphobia. In addition, Lydiard and Ballenger (1987) noted that monoamine oxidase inhibitors (MAOIs) may be superior to TCAs. Although MAOIs may still be the best treatment for some patients, the overall role of MAOIs in managing anxiety disorders is now fairly small because of their potential side effects and drug-drug interactions. The role of the safer

reversible inhibitors of monoamine oxidase A (not available in the United States) in panic disorder is unclear.

Other Drugs

Mirtazapine, a noradrenergic and specific serotonergic antidepressant, demonstrated possible benefit in panic disorder in open trials (Boshuisen *et al.* 2001; Sarchiapone *et al.* 2003) and in a double-blind comparison with fluoxetine (Ribeiro *et al.* 2001). However, double-blind, placebo-controlled trials have yet to be conducted. It is noteworthy that mirtazapine has been associated with the induction of panic attacks in patients with depression undergoing dosage escalation and discontinuation (Berigan 2003; Klesmer *et al.* 2000).

Vortioxetine is a novel atypical antidepressant considered to have a multimodal mechanism of action. This drug demonstrated clinical efficacy in panic disorder in an open-label trial (Shah and Northcutt 2018) but has not been studied in double-blind, placebo-controlled trials.

The 5-HT_{1A} partial agonist buspirone and the anticonvulsant gabapentin were generally ineffective in panic disorder, although gabapentin showed superiority to placebo in a subgroup of patients with severe illness (Pande *et al.* 2000; Sheehan *et al.* 1990). Possible benefit has been reported in open-label trials for other anticonvulsant drugs, including levetiracetam, tiagabine, and valproic acid (Keck *et al.* 1993; Papp 2006; Zwanzger *et al.* 2001). A small double-blind, placebo-controlled trial with tiagabine did not show clinical benefits, although cholecystokinin-tetrapeptide (CCK-4)-induced sensitivity to panic attacks decreased (Zwanzger *et al.* 2009).

Preliminary data suggest that improvement in refractory panic disorder occurs when atypical antipsychotics, such as olanzapine (Sepede *et al.* 2006) or risperidone (Simon *et al.* 2006), are used to augment SSRI treatment or are taken in higher dosages as monotherapy (e.g., olanzapine [Hollifield *et al.* 2005]). In a 2013 randomized, placebo-controlled monotherapy trial of extended-release quetiapine versus divalproex for patients with bipolar disorder and comorbid panic or generalized anxiety disorder, extended-release quetiapine (50-300 mg/day) showed rapid and sustained effects in reducing anxiety symptoms (Sheehan *et al.* 2013). However, a 2015 double-blind, placebo-controlled trial in which extended-release quetiapine was coadministered with an SSRI to patients with SSRI-resistant panic disorder did not support the efficacy of this treatment strategy (Goddard *et al.* 2015).

A 2017 double-blind, randomized placebo-controlled trial of D-cycloserine, a partial *N*-methyl-D-aspartate receptor agonist that potentially augments response to exposure therapy in anxiety disorders, did not demonstrate this effect of improved response to exposure therapy for panic disorder (Hofmeijer-Sevink *et al.* 2017).

Long-Term Management

Maintenance treatment is recommended for at least 12-24 months, if not longer. In a controlled trial of paroxetine, clomipramine, and placebo, 84% of paroxetine-treated patients eventually became panic free over the 9-month study period (Lecrubier *et al.* 1997b). In a 4-year naturalistic follow-up study of 367 patients with panic disorder, greater improvements in panic attacks, phobic avoidance, and daily functioning were observed for those who received continuation treatment for 4 years compared with 1 year (Katschnig *et al.* 1995), suggesting that recovery can continue over several years.

Long-term randomized controlled trials have reported efficacy for citalopram (Lepola *et al.* 1998), clomipramine (Fahy *et al.* 1992), fluoxetine (Michelson *et al.* 1999), paroxetine (Lecrubier *et al.* 1997b; Lydiard *et al.*

1998), and sertraline (Rapaport *et al.* 2001). In a relapse prevention trial following 3 months of successful open-label treatment, Ferguson *et al.* (2007) showed that over the course of 7 months, the rate of relapse with extended-release venlafaxine was 22%, compared with 50% for placebo.

Discontinuation Symptoms

Although there is some similarity between symptoms of relapse and drug withdrawal, the existence of discontinuation symptoms is indisputable. When a decision is made to stop, a slow taper over several weeks is recommended for all antidepressants or other medications being used to treat panic disorder; for some benzodiazepines, it may be necessary to taper the drug over weeks or months. Timing of the taper may be important--it is best done when other variables in a patient's life are as stable as possible. Approaches such as switching to a longer-acting benzodiazepine (e.g., clonazepam), adding an anticonvulsant (e.g., carbamazepine or valproate [Pages and Ries 1998]), and utilizing CBT (Otto *et al.* 1993) have all been used to ameliorate discontinuation symptoms.

Nonpharmacological Approaches

Various elaborations of CBT have demonstrated consistent efficacy for panic disorder, with the common elements being education, cognitive strategies, and exposure to feared sensations and situations (Kaczkurkin and Foa 2015; Pompoli *et al.* 2016). CBT is a first-line choice; even when pharmacotherapy is given as the main treatment, principles of CBT should be incorporated into the management plan. CBT can be of benefit during the process of drug discontinuation and may also lessen the chance of relapse afterward.

Social Anxiety Disorder

Social anxiety disorder (known as social phobia in DSM-IV [American Psychiatric Association 1994]) has a lifetime prevalence of 12% (Kessler *et al.* 2005b). This disorder can be grouped into two types: *generalized* (a term used in DSM-IV but removed in DSM-5 [American Psychiatric Association

2013]) and *nongeneralized* (a performance-only specifier, according to DSM-5). Generalized social anxiety disorder is more common in clinical settings, is usually more disabling, and is associated with greater comorbidity and genetic loading. Most of our knowledge about pharmacotherapy for social anxiety disorder derives from the generalized type, and the literature suggests that different medication approaches may be called for in treating the two subtypes. Social anxiety disorder as described in this section refers to what DSM-IV described as *generalized* social anxiety disorder.

Treatment of social anxiety disorder involves multiple components. For example, treatment requires that 1) symptoms of fear, avoidance, and physiological distress are brought under control; 2) comorbidity is treated; 3) disability and impairment are improved; and 4) quality of life is enhanced. Furthermore, evidence from maintenance and relapse prevention studies has confirmed the value of long-term therapy in treatment responders.

Instruments commonly used to measure treatment response in social anxiety disorder include the clinician-and self-rated versions of the Liebowitz Social Anxiety Scale (Liebowitz 1987), which assesses 24 performance or interpersonal situations for fear and avoidance. A score of 30 or less is considered to equate with remission. The Social Phobia Inventory is a 17-item self-rating instrument that assesses fear, avoidance, and physiological distress (Connor *et al.* 2000) and, like the Liebowitz Social Anxiety Scale, can also be used to measure improvement.

Pharmacotherapy

Most clinicians consider SSRIs and venlafaxine as the first choice for treatment of social anxiety disorder. Second-line drugs include benzodiazepines, other antidepressants (e.g., mirtazapine, MAOIs), and some other drug types (e.g., gabapentin, pregabalin). For performance-only social anxiety disorder, b-blockers or benzodiazepines are considered the first choice.

Serotonergic Drugs

Paroxetine, controlled-release paroxetine, sertraline, controlled-release fluvoxamine, and extended-release venlafaxine are currently FDA approved for the treatment of social anxiety disorder.

In meta-analyses, SSRIs were superior to placebo in terms of response rates and reductions in symptoms, disability, and relapse (Hedges *et al.* 2007; van der Linden *et al.* 2000; Williams *et al.* 2017). The superiority of extended-release venlafaxine over placebo was also shown in two double-blind trials of social anxiety disorder treatment (Allgulander *et al.* 2004b; Liebowitz *et al.* 2005).

A double-blind, placebo-controlled trial of mirtazapine in women showed statistically significant superiority for the drug over placebo (Muehlbacher *et al.* 2005). However, another double-blind, placebo-controlled trial in 60 outpatients with social anxiety disorder who received mirtazapine (30-45 mg/day) failed to demonstrate evidence of efficacy (Schutters *et al.* 2010).

Benzodiazepines

Three major placebo-controlled trials have shown efficacy for benzodiazepines in social anxiety disorder. Gelernter *et al.* (1991) showed a modest increase in response rates for alprazolam over placebo (38% vs. 20%) at a mean dosage of 4.2 mg/day, although alprazolam was generally inferior to phenelzine. Davidson *et al.* (1993) found a substantially greater response rate for clonazepam compared with placebo (70% vs. 20%) in 75 subjects. Bromazepam was also more effective than placebo (Versiani *et al.* 1997). In a double-blind, placebo-controlled trial of augmentation and switch strategies for refractory social anxiety disorder, Pollack *et al.* (2014) found that clonazepam augmentation ([?] 3 mg/day) of sertraline treatment was superior to placebo augmentation and also superior to a switch to venlafaxine, with a higher percentage of patients taking clonazepam plus sertraline achieving remission.

Benzodiazepines provide significant benefits, yet they are not considered first-line drugs because of their more limited spectrum of action (i.e., they are not expected to improve depressive symptoms, which are commonly comorbid in patients with social anxiety disorder) and potential withdrawal difficulties. However, they work rapidly,

are well tolerated, and may be particularly useful for individuals with periodic performance-related anxiety or treatment-resistant social anxiety disorder.

Gabapentin and Pregabalin and Anticonvulsants

Gabapentin and pregabalin produce significant effects in social anxiety disorder. Pande *et al.* (1999) found a superior effect for gabapentin over placebo in a trial using flexible dosing (900-3,600 mg/day, with 2,100 mg/day being the most common final gabapentin dosage), with response rates of 39% and 17%, respectively. Pregabalin also has shown benefit in social anxiety disorder (Feltner *et al.* 2003; Pande *et al.* 2003). Although pregabalin 150 mg/day was no different from placebo, 600 mg/day produced greater effects than placebo, with response rates of 43% and 22%, respectively. A 26-week double-blind, placebo-controlled maintenance trial of pregabalin at a fixed dosage of 450 mg/day showed that pregabalin not only was superior to placebo in maintaining symptomatic improvement but also was relatively well tolerated (Greist *et al.* 2011). Levetiracetam failed to differentiate from placebo (Stein *et al.* 2010). Further work with anticonvulsants is needed, given that these agents are generally well tolerated, safe, and less likely to produce discontinuation symptoms compared with many SSRIs and benzodiazepines.

Monoamine Oxidase Inhibitors

Reversible inhibitors of monoamine oxidase A. Moclobemide, a reversible inhibitor of monoamine type A, is safer than older MAOIs and was shown to be almost as effective as phenelzine and significantly better than placebo (Versiani *et al.* 1992), but it is not marketed in the United States.

Irreversible inhibitors of monoamine oxidase. Phenelzine showed positive benefit in four studies (Gelernter *et al.* 1991; Heimberg *et al.* 1998;

Liebowitz *et al.* 1992; Versiani *et al.* 1992). Response rates for phenelzine were 69%, 85%, 64%, and 65%, respectively, compared with 20%, 15%, 23%, and 33% for placebo; phenelzine overall was shown to have a large effect size (Davis *et al.* 2014). MAOIs (phenelzine or tranylcypromine) should be strongly considered for individuals whose symptoms are nonresponsive to other treatments and who can adhere to the necessary dietary and medication restrictions.

Other Drugs

Olanzapine yielded greater improvement than placebo in a small (*n* = 12) double-blind, placebo-controlled monotherapy trial (Barnett *et al.* 2002). This finding suggests that atypical antipsychotics may deserve further investigation in social anxiety disorder, although their benefits must be weighed against their potential metabolic adverse effects. Although the 5-HT_3 antagonist ondansetron produces a statistically significant effect relative to placebo, it seems to be of limited clinical benefit (Bell and DeVeaugh-Geiss 1994; Davidson *et al.* 1997) but may be used adjunctively in some cases. Buspirone was ineffective in a double-blind trial, with a 7% response rate (van Vliet *et al.* 1997).

Despite their intuitive appeal, b-blockers have shown poor efficacy in treating social anxiety disorder (other than for the performance-only specifier). For example, atenolol failed to separate from placebo in two trials (Liebowitz *et al.* 1992; Turner et al. 1994). b-Blockers do show some value in performance-related social anxiety, perhaps by virtue of their ability to reduce peripheral autonomic arousal and block negative feedback.

Despite earlier studies showing promise for the use of D-cycloserine augmentation of exposure therapy in social anxiety disorder (Guastella *et al.* 2008; Hofmann *et al.* 2006), findings in subsequent studies have been far less encouraging overall (Hofmann *et al.* 2013, 2019; Roque *et al.* 2018).

Connor *et al.* (2006) reported benefit for one-time intradermal bilateral axillary injections of botulinum toxin type A (50 units) for individuals with social anxiety disorder and troublesome axillary hyperhidrosis. The effects persisted over 8 weeks and were superior to placebo for sweating, daily function, and activities. All subjects received concomitant paroxetine for other aspects of social anxiety disorder.

A 4-week Phase III pilot randomized double-blind, placebo-controlled crossover study showed that as-needed use of intranasal PH94B (3b-androsta-4,16-dien-3-ol), a synthetic neurosteroid molecule, was superior to placebo for subjective distress in social anxiety disorder (Liebowitz *et al.* 2016). Further studies on the abuse potential and long-term effects of PH94B are needed to clarify its full utility for social anxiety disorder.

Treatment in Children and Adolescents

Pharmacological approaches to treating social anxiety disorder in children are usually implemented when behavioral approaches have been insufficient to resolve symptoms and improve functioning. One placebo-controlled trial of fluvoxamine in children ages 6-17 years showed that this agent was superior to placebo for social anxiety disorder, generalized anxiety disorder, and their combination: 76% of the fluvoxamine group achieved response, compared with 19% of the placebo group (Walkup *et al.* 2001). Double-blind trials of immediate-release paroxetine (Wagner *et al.* 2004) and extended-release venlafaxine (March *et al.* 2007) have produced positive results in children and adolescents with social anxiety disorder.

A multisite study compared CBT alone, sertraline alone, combination CBT and sertraline, and placebo in 488 children (ages 7-17 years) with a primary diagnosis of separation anxiety disorder, generalized anxiety disorder, or social anxiety disorder (Walkup *et al.* 2008). CBT monotherapy and sertraline monotherapy were each superior to placebo in reducing anxiety symptoms in children (response rates of 59.7% and 54.9%, respectively); however, the combination treatment had the best response rate (80.7% [Walkup *et al.* 2008]). At 24 and 36 weeks of follow-up, the majority of acute responders maintained their response, and the combination treatment maintained its advantage over the CBT and sertraline monotherapies (Piacentini *et al.* 2014).

Treatment Duration

Social anxiety disorder is a chronic illness, and long-term treatment is generally recommended. Sutherland *et al.* (1996) reported that at 2-year follow-up, subjects who received active drug rather than placebo had improved. To date, relatively few relapse prevention studies have been done. In a 12-month trial with clonazepam, Connor *et al.* (1998) showed a 20% relapse rate for those switched to placebo compared with 0% for those who continued clonazepam. Stein *et al.* (1996) reported that 62% of subjects experienced relapse when switched double-blind from paroxetine to placebo after 12 weeks, compared with only 12% of patients whose symptoms relapsed during maintenance treatment with paroxetine. More research is needed to determine the optimal duration of medication treatment for social anxiety disorder; personalizing this dimension of care will be particularly important.

Other Issues

CBT is efficacious for social anxiety disorder and is comparable in efficacy to pharmacotherapy (Davidson *et al.* 2004b; Fedoroff and Taylor 2001), but little is known regarding whether adding CBT to medication lowers the relapse rate. In a comparative study of drug treatment and psychotherapy, Heimberg *et al.* (1998) showed that phenelzine and CBT were approximately similar, although phenelzine was more effective for patients with more severe symptoms. When subjects who had discontinued treatment were followed up, rates of relapse tended to be lower for those who had received CBT than for those who had taken phenelzine. A later study by the same group (Blanco *et al.* 2010) showed superior outcomes for combined phenelzine and CBT over each treatment given alone. Additionally, in children with anxiety disorders, including social anxiety disorder, the combination of CBT and sertraline demonstrated superior response rates compared with both monotherapies (Walkup *et al.* 2008).

Specific Phobia

Specific phobia is among the most common psychiatric disorders, with a lifetime prevalence of 8%-12.5% and a 12-month prevalence of 3.5%-9% (Alonso *et al.* 2004; Kessler *et al.* 2005a, 2005b). Although the disorder is characterized by an early onset (median age at onset = 7 years [Kessler *et al.* 2005b]), most individuals are unimpaired by their symptoms and rarely seek treatment (Magee *et al.* 1996; Stinson *et al.* 2007; Zimmerman and Mattia 2000). However, for a minority of individuals, specific phobia causes significant disability and requires treatment. The generally accepted treatment of choice is exposure therapy, which is uniformly and rapidly effective, with techniques including virtual reality as well as in vivo exposure and muscle tension exercises (for blood-injury phobia) (Canadian Psychiatric Association 2006). Few studies have evaluated the efficacy of pharmacological approaches, and no drug has yet been FDA approved for the treatment of specific phobia. No standard ratings exist for this disorder, although the Marks-Mathews Fear Questionnaire is quite suitable for blood-injury phobia and some other fears. A modification of this scale, the Marks-Sheehan Main Phobia Severity Scale (Sheehan 1986), can be recommended.

Serotonergic drugs have shown efficacy in treating symptoms of fear and avoidance in a variety of anxiety disorders and thus would seem logical choices in specific phobia. In a small 4-week double-blind controlled trial (*N* = 11), subjects receiving paroxetine ([?] 20 mg/day) had a 60% response rate compared with 17% for subjects receiving placebo (Benjamin *et al.* 2000). A randomized double-blind pilot trial compared escitalopram versus placebo over 12 weeks in 12 adults with specific phobia (Alamy *et al.* 2008). No difference in the primary outcome was observed; however, 60% of escitalopram-treated patients showed response (based on a Clinical Global Impression Scale improvement score of 1 or 2), compared with 29% of patients receiving placebo (effect size = 1.13). The findings from these two small trials require validation in larger controlled trials. In contrast, in a controlled trial of the serotonergic and noradrenergic TCA imipramine in 218 individuals with phobic disorders (agoraphobia, mixed phobia, or simple phobia) receiving 26 weeks of behavior therapy, no difference was observed between imipramine and placebo (Zitrin *et al.* 1983). The use of SSRIs for specific phobia is limited by the necessity to take these medications regularly (i.e., they are not useful prn).

In a long-term controlled study of clonazepam in DSM-III-TR (American Psychiatric Association 1987) social phobia, Davidson *et al.* (1994) observed that clonazepam was superior to placebo in reducing symptoms of anxiety related to blood-injury phobia, as measured by changes in the blood-injury phobia subscale of the Marks-Mathews Fear Questionnaire. Intermittent use of benzodiazepines also may be helpful in the acute treatment of the somatic anxiety that accompanies specific phobia, although this usage has not been an area of active investigation.

Using a novel approach, Ressler *et al.* (2004) investigated the effect of a cognitive enhancer, D-cycloserine, as an adjunct to psychotherapy. D-Cycloserine is an *N*-methyl-D-aspartate receptor partial agonist that has demonstrated improvement in extinction in rodents. Subjects with acrophobia ($n = 28$) were randomly assigned to a single dose of D-cycloserine or placebo before each of two virtual reality exposure therapy sessions. The combination of D-cycloserine and exposure therapy was associated with greater improvement in the virtual reality setting as well as on a variety of anxiety domains. These changes were noted early in treatment and were maintained at 3-month follow-up. However, other randomized controlled studies of D-cycloserine in specific phobia, including acrophobia and spider phobia, have yielded inconsistent but mostly negative findings for D-cycloserine compared with placebo (Guastella *et al.* 2007; Gutner *et al.* 2012; Kappelmann *et al.* 2020; Tart *et al.* 2013).

Generalized Anxiety Disorder

Generalized anxiety disorder is common, with a lifetime prevalence of 5%-6% (Wittchen and Hoyer 2001). In the primary care setting, it is the most prevalent anxiety disorder, with rates that exceed 8% (Goldberg and Lecrubier 1995). Generalized anxiety disorder tends to be chronic and disabling, with lifetime rates of comorbidity as high as 90% (Blanco *et al.* 2014)--particularly for depression, with a prevalence rate greater than 60%--which can increase the severity and burden of the disorder. Unlike for other anxiety disorders, the prevalence of generalized anxiety disorder tends to increase with age, with a lifetime prevalence of 11% in individuals older than 65 years and late-life onset occurring in at least 25% of cases (Zhang *et al.* 2015).

In most generalized anxiety disorder pharmacotherapy trials, the clinician-administered Hamilton Anxiety Scale (Ham-A; Hamilton 1959) has been used to assess patient symptoms. The Ham-A measures psychic and somatic symptoms of anxiety; remission is usually defined as a Ham-A score of 7 or less. The self-rated Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983) is also widely used and is capable of detecting differences in treatment efficacy.

Pharmacotherapy

SSRIs and SNRIs are considered the first-line pharmacological treatment for generalized anxiety disorder. However, additional pharmacological approaches--including other antidepressants, anxiolytics, anticonvulsants, and other drugs--can also be considered. Drugs that have been approved in the United States for the treatment of generalized anxiety disorder or historical forerunners of the disorder include a large number of benzodiazepines, buspirone, immediate-release paroxetine, escitalopram, extended-release venlafaxine, and duloxetine. Pregabalin is not approved for generalized anxiety disorder in the United States but is approved for this indication in Europe. For a comparison of pharmacological treatments for generalized anxiety disorder, see the later section "Comparative Efficacy of Pharmacological, Psychological, and Combination Treatments."

Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors

Meta-analyses have presented varying results regarding the efficacy and tolerability of each SSRI in generalized anxiety disorder. Nevertheless, within the clinical context, all SSRIs are considered to have comparable efficacy.

In one study, immediate-release paroxetine (20-50 mg/day) was as effective as imipramine and more effective than 2'-chlordesmethyldiazepam (Rocca *et al.* 1997). Compared with placebo, a similar dosage range of immediate-release paroxetine was associated with a significantly greater reduction in anxiety after 8 weeks of treatment (Pollack *et al.* 2001; Rickels *et al.* 2003), with an improvement in Ham-A-rated psychic anxiety observed as early as 1 week after treatment initiation (Pollack *et al.* 2001). Immediate-release paroxetine also improved social functioning in patients with generalized anxiety disorder (Pollack *et al.* 2001).

Escitalopram (10-20 mg/day) was superior to placebo in improving anxiety symptoms, disability, or quality of life in three 8-week trials (Davidson *et al.* 2004a; Goodman *et al.* 2005). In addition, escitalopram was equivalent to immediate-release paroxetine in a 6-month trial (Bielski *et al.* 2005). In a larger placebo-controlled trial, escitalopram (10 mg/day) was superior to paroxetine (20 mg/day), and both escitalopram dosages of 10 and 20 mg/day were superior to placebo (Baldwin *et al.* 2006). In a relapse prevention study, Allgulander *et al.* (2006) found that sustained treatment with escitalopram (20 mg/day) for up to 74 weeks reduced the relapse rate (19%) relative to placebo substitution (56%).

Sertraline was demonstrated to be superior to placebo in generalized anxiety disorder in 12-week (Allgulander *et al.* 2004a) and 10-week (Brawman-Mintzer *et al.* 2006) double-blind, placebo-controlled trials. Sertraline was well tolerated and showed beneficial effects on Ham-A-rated psychic and somatic anxiety symptoms compared with placebo (Dahl *et al.* 2005).

Several placebo-controlled trials have confirmed the short-term efficacy of extended-release venlafaxine in treating both psychic and somatic symptoms of generalized anxiety disorder over 8 weeks. In a trial of 365 adult outpatients treated with extended-release venlafaxine (75 or 150 mg/day), buspirone (30 mg/day), or placebo, mean Ham-A-adjusted scores on the anxiety and tension items were significantly more improved with both active drug dosages compared with placebo (Davidson *et al.* 1999). In addition, extended-release venlafaxine was superior to buspirone on the Hospital Anxiety and Depression Scale anxiety subscale (Davidson *et al.* 1999). In a second trial of 541 outpatients taking either extended-release venlafaxine (37.5, 75, or 150 mg/day) or placebo (Allgulander *et al.* 2001), the 75 mg/day and 150 mg/day dosages showed superior efficacy on all primary outcome measures compared with placebo (with improvement in psychic anxiety noted earlier than somatic symptoms), whereas the 37.5 mg/day dosage was superior to placebo on only one measure (the Hospital Anxiety and Depression Scale anxiety subscale). In a third trial of fixed extended-release venlafaxine (75, 150, or 225 mg/day [Rickels *et al.* 2000]), the drug was superior to placebo on all outcome measures, with the most robust effects observed at 225 mg/day. Extended-release venlafaxine significantly reduced psychic anxiety but not somatic symptoms.

Extended-release venlafaxine also has shown long-term efficacy for generalized anxiety disorder (Allgulander *et al.* 2001; Gelenberg *et al.* 2000). Additionally, extended-release venlafaxine is also effective in treating generalized anxiety disorder with comorbid depression (Silverstone and Salinas 2001). The response was delayed somewhat in subjects with comorbid generalized anxiety disorder and depression compared with those with depression alone, suggesting that individuals with comorbidity may benefit from a longer course of treatment.

Duloxetine, another SNRI antidepressant, has shown superior efficacy to placebo in generalized anxiety disorder (Allgulander *et al.* 2007; Rynn *et al.* 2008) in the dosage range of 60-120 mg/day and also seems to lessen the chance of relapse during maintenance therapy. A randomized placebo-controlled, flexible-dose study demonstrated that duloxetine was effective and well tolerated in the treatment of generalized anxiety disorder in children and adolescents ages 7-17 years (Strawn *et al.* 2015).

An interesting application of SSRIs in generalized anxiety disorder is in combination with nonbenzodiazepine hypnotics such as eszopiclone (Pollack *et al.* 2008a) and zolpidem (Fava *et al.* 2009), which may be particularly suited when insomnia is a major problem.

Anxiolytics

Benzodiazepines. Benzodiazepines have been widely used to treat acute and chronic anxiety since their introduction in the 1960s. Their activity is mediated through potentiation of the inhibitory neurotransmitter GABA at the $GABA_A$ receptor. The efficacy and relative safety of short-term benzodiazepine use (e.g., several weeks or months) is well established (Rickels *et al.* 1983; Shader and Greenblatt 1993). However, longer-term use of these drugs is more controversial and may be associated with the development of tolerance, physiological dependence, and withdrawal (if abruptly discontinued) as well as troublesome side effects including ataxia, sedation, motor dysfunction, and cognitive impairment. Furthermore, these drugs should be avoided in patients with a history of substance use disorders, and long-term use may infrequently lead to the development of major depressive disorder (Lydiard *et al.* 1987).

Benzodiazepines have been shown to be effective in generalized anxiety disorder, as reported by Rickels *et al.* (1993). The appeal of these drugs lies in their rapid onset of action, ease of use, tolerability, and relative safety. Findings from several 6-to 8-month trials of maintenance treatment for chronic anxiety have indicated continued efficacy of benzodiazepines over time (Rickels *et al.* 1983, 1988a, 1988b; Schweizer *et al.* 1993). Because generalized anxiety disorder tends to be chronic, many patients may need to continue pharmacotherapy with benzodiazepines (or other drugs) for many years, and long-term use of benzodiazepines may lead to the complications listed earlier.

Approximately 70% of patients with generalized anxiety disorder will respond to an adequate trial of a benzodiazepine (Greenblatt *et al.* 1983), which corresponds to the equivalent of a 3-to 4-week treatment course of diazepam ([?] 40 mg/day) or alprazolam (4 mg/day [Schweizer and Rickels 1996]). Discontinuation should be managed by slow taper to minimize withdrawal symptoms, rebound anxiety, and relapse potential. Some evidence suggests that benzodiazepines may be more effective in treating the autonomic arousal and somatic symptoms of generalized anxiety disorder but less effective for the psychic symptoms of worry and irritability (Rickels *et al.* 1982; Rosenbaum *et al.* 1984).

As our understanding of the phenomenology of generalized anxiety disorder has grown, there has been a greater emphasis on the psychic (e.g., worry) component of the disorder (American Psychiatric Association 2013). Given these changes, along with the high rates of comorbid depression in generalized anxiety disorder and the anxiolytic activity of many of the newer classes of antidepressants, the use of benzodiazepines as a primary treatment for generalized anxiety disorder is less recommended.

Azapirones. The azapirones are believed to exert their anxiolytic effect through partial agonism of 5-HT_{1A} receptors. A Cochrane Review of randomized controlled trials of azapirones in generalized anxiety disorder suggested that these agents are relatively well tolerated and effective, particularly for patients not previously treated with benzodiazepines (Chessick *et al.* 2006). An adequate trial of buspirone in generalized anxiety disorder would be 3-4 weeks of treatment at a dosage of up to 60 mg/day, in divided doses. Treatment-limiting effects of the drug include a greater potential for side effects at higher dosages, slower onset of action, more variable antidepressant effects, and possibly reduced effectiveness in patients with a prior favorable response to benzodiazepines (Chessick *et al.* 2006; Schweizer *et al.* 1986).

Tricyclic Antidepressants

Imipramine is recommended as a second-line pharmacological option for generalized anxiety disorder because of its adverse effects, although there is significant evidence for its benefits (Rickels and Rynn 2002).

Other Antidepressants

The antidepressant mirtazapine also has demonstrated anxiolytic properties (Ribeiro *et al.* 2001). However, published reports of its effects in generalized anxiety disorder are limited to a small open-label study in major depressive disorder and comorbid generalized anxiety disorder (Goodnick *et al.* 1999) and a small open-label generalized anxiety disorder trial in 44 outpatients (Gambi *et al.* 2005). Although the results were encouraging, data from controlled trials are needed to adequately assess a possible role for mirtazapine in generalized anxiety disorder.

In a 12-week double-blind active comparison trial of extended-release bupropion (150-300 mg/day) versus escitalopram (10-20 mg/day) in 24 subjects, Bystritsky *et al.* (2008) found similar Ham-A-rated anxiolytic efficacy for both medications.

A meta-analysis showed that vortioxetine was superior to placebo in the treatment of generalized anxiety disorder, especially for severe illness (Pae *et al.* 2015). However, a subsequent meta-analysis failed to confirm this finding (Qin *et al.* 2019). Although vortioxetine was well tolerated, it did not significantly improve response rates compared with placebo. Larger controlled trials are needed to further assess the efficacy of vortioxetine in generalized anxiety disorder.

In a meta-analysis of three randomized controlled trials, vilazodone was superior to placebo in the short-term treatment of generalized anxiety disorder (Zareifopoulos and Dylja 2017). A recent network meta-analysis also showed efficacy of vortioxetine in generalized anxiety disorder (He *et al.* 2019). However, in both analyses, vortioxetine had a higher incidence of adverse events and worse acceptability than placebo. Long-term maintenance studies are needed to evaluate the safety profile of this drug.

Pregabalin and Anticonvulsants

The a_2d calcium channel antagonist pregabalin was superior to placebo in four studies of generalized anxiety disorder (Feltner *et al.* 2003; Pande *et al.* 2003; Pohl *et al.* 2005; Rickels *et al.* 2005). Efficacy was noted early in treatment, but the ability of this drug to successfully treat some of the comorbid disorders associated with generalized anxiety disorder is unknown. A review of six short-term, double-blind, placebo-controlled pregabalin trials in generalized anxiety disorder showed that pregabalin treatment significantly improved both psychic and somatic Ham-A-rated generalized anxiety disorder symptoms, with a dose-response effect that plateaued at 300 mg/day (Lydiard *et al.* 2010). For elderly patients with generalized anxiety disorder, pregabalin has shown efficacy and reasonably good tolerability (Montgomery 2006). In a long-term trial in 624 patients with generalized anxiety disorder, responders to 8 weeks of open-label pregabalin (450 mg/day) were randomly assigned to pregabalin or placebo for 24 weeks (Feltner *et al.* 2008). Relapse rates were significantly lower for pregabalin than for placebo (42% vs. 65%), although attrition rates for pregabalin were higher (21.4% vs. 15.3%).

As noted in a case report (Markota and Morgan 2017), the clinical utility of gabapentin has been under consideration. Nevertheless, there are no published controlled studies examining the efficacy of gabapentin for generalized anxiety disorder.

The GABA reuptake inhibitor tiagabine failed to separate from placebo on key measures in three placebo-controlled multicenter trials (Pollack *et al.* 2008b).

Antipsychotics

Evidence for antipsychotic monotherapy in generalized anxiety disorder is limited for some agents and more robust for others. Currently, the strongest evidence supporting atypical antipsychotic use in generalized anxiety disorder is for extended-release quetiapine. This agent was shown to be effective and superior to placebo in a multicenter trial, and a dosage of 150 mg/day was effective for both psychic and somatic anxiety symptoms, with improvement being noted as early as 4 days after initiation of treatment (Bandelow *et al.* 2010). Another 8-week randomized controlled trial also demonstrated the efficacy of extended-release quetiapine (150 and 300 mg/day) in generalized anxiety disorder (Merideth *et al.* 2012). In a longer-term double-blind, placebo-controlled multicenter maintenance trial, extended-release quetiapine (50-300 mg/day) was effective in preventing the recurrence of anxiety symptoms (Katzman *et al.* 2011).

Antipsychotics have also been examined as augmentation options for patients with treatment-resistant generalized anxiety disorder who show a less-than-adequate response to antidepressants or anxiolytics. In a 5-week, double-blind, placebo-controlled trial, low-dose adjunctive risperidone was effective in reducing Ham-A scores (Brawman-Mintzer *et al.* 2005). Aripiprazole augmentation for treatment-resistant generalized anxiety disorder also showed promising results in two small open-label 6-to 8-week trials (Hoge *et al.* 2008; Menza *et al.* 2007). One 6-week randomized placebo-controlled study showed that olanzapine augmentation resulted in a greater proportion of responders with treatment-resistant generalized anxiety disorder, although there were no statistically significant differences from placebo in Ham-A scores (Pollack *et al.* 2006). Whereas one 8-week randomized placebo-controlled trial (not double-blind) demonstrated efficacy of quetiapine augmentation (Altamura *et al.* 2011), two 8-week double-blind, randomized placebo-controlled trials with larger samples did not report efficacy (Khan *et al.* 2013; Simon *et al.* 2008). A randomized placebo-controlled trial did not report efficacy of ziprasidone in treatment-resistant generalized anxiety disorder (Lohoff *et al.* 2010).

Long-term use of atypical antipsychotics carries concerns about tolerability and safety, especially in regard to weight gain and metabolic adverse effects. These concerns must be balanced against the long-term benefits of their use for generalized anxiety disorder in terms of reduced disability and improved functionality.

Hydroxyzine

Hydroxyzine blocks histamine$_1$ and muscarinic receptors. In three controlled trials, hydroxyzine was superior to placebo (Ferreri and Hantouche 1998; Lader and Scotto 1998; Llorca *et al.* 2002). In a Cochrane Review comparing hydroxyzine with other anxiolytic agents such as benzodiazepines and buspirone, hydroxyzine was equivalent in tolerability, efficacy, and acceptability for the treatment of generalized anxiety disorder (Guaiana *et al.* 2010). In Europe, previous reports of hydroxyzine-related ventricular arrhythmias led to cautionary labeling regarding the use of hydroxyzine, and the maximum dosage for this drug is restricted to 100 mg/day (European Medicines Agency 2015).

Other Drugs

Riluzole, a presynaptic glutamate release inhibitor, showed promise in a small open-label study at a dosage of 100 mg/day (Mathew *et al.* 2005) but has not been studied in placebo-controlled, double-blind studies.

Agomelatine, a 5-HT$_{2C}$ receptor antagonist and melatonin$_{1/2}$ receptor agonist, was efficacious in the short-term treatment of generalized anxiety disorder (Stein *et al.* 2014, 2008) and was effective and well tolerated in longer-term treatment (Stein *et al.* 2012). This drug is not available in the United States.

Complementary Treatments

Complementary treatments have had mixed results for generalized anxiety disorder. Homeopathy was ineffective in one trial (Bonne *et al.* 2003). The herbal remedy kava did not separate from placebo in one trial (Connor and Davidson 2002), although Sarris *et al.* (2009) showed some evidence supporting the benefit of a water-soluble formulation of kava in subjects with short-term generalized anxiety disorder-like symptoms. Liver damage remains a potentially devastating concern, however, and even the preferred aqueous extract cannot be regarded as entirely safe, particularly at kava dosages greater than 250 mg/day (Teschke and Schulze 2010). Two small placebo-controlled

trials suggested that chamomile and Ginkgo biloba may have modest anxiolytic effects in patients with mild to moderate generalized anxiety disorder (Amsterdam *et al.* 2009; Woelk *et al.* 2007). Kasper *et al.* (2014) demonstrated that lavender oil extract at dosages of 80 and 160 mg/day was superior to placebo and was better tolerated than paroxetine in a four-arm trial of patients with DSM-5 generalized anxiety disorder. Later studies by these researchers showed that the compound reduced 5-HT$_{1A}$ receptor binding in the hippocampus, anterior cingulate cortex, and fusiform and temporal gyri (Baldinger *et al.* 2014).

Comparative Efficacy of Pharmacological, Psychological, and Combination Treatments

In a meta-analysis of generalized anxiety disorder studies, Hidalgo *et al.* (2007) reported effect sizes for each drug or drug group versus placebo. These effect sizes were as follows (in diminishing order from largest to smallest): pregabalin, 0.50; hydroxyzine, 0.45; extended-release venlafaxine, 0.42; benzodiazepines, 0.38; SSRIs, 0.36; buspirone, 0.17; and homeopathy and herbal treatment, [?] 0.31. In another meta-analysis, it was uncertain whether antidepressant drugs, benzodiazepines, and pregabalin differed in their relative efficacy in reducing the severity of psychic or somatic anxiety symptoms in generalized anxiety disorder (Baldwin *et al.* 2011). A more recent network meta-analysis showed that duloxetine, venlafaxine, escitalopram, and pregabalin were more efficacious than placebo, with relatively good acceptability (Slee *et al.* 2019). Mirtazapine, sertraline, fluoxetine, buspirone, and agomelatine were also efficacious and well tolerated, but these findings were limited by small sample sizes. Quetiapine, paroxetine, and benzodiazepines were effective but poorly tolerated compared with placebo. Among these agents, quetiapine had the largest effect on Ham-A scores (Slee *et al.* 2019). In another network meta-analysis that compared SSRIs, SNRIs, and newer antidepressants (vilazodone, levomilnacipran, and vortioxetine), all of the drugs except fluoxetine and vortioxetine were more effective than placebo, with duloxetine and escitalopram showing the greatest efficacy among these (He *et al.* 2019).

Medications that have been approved in the United States for the treatment of generalized anxiety disorder or historical forerunners of the disorder include a large number of benzodiazepines, buspirone, immediate-release paroxetine, escitalopram, extended-release venlafaxine, and duloxetine. Pregabalin is not approved for treatment of generalized anxiety disorder in the United States but is approved for this indication in Europe.

There is also convincing evidence in favor of efficacy for CBT in generalized anxiety disorder, with sustained benefit over 2 years of follow-up (for a review, see Canadian Psychiatric Association 2006). A Cochrane Review reported that CBT was more effective in reducing anxiety symptoms in short-term treatment of generalized anxiety disorder compared with treatment as usual or waiting-list control conditions (Hunot *et al.* 2007). There are no randomized controlled studies that compare, or combine, CBT and pharmacotherapy in generalized anxiety disorder

(Bandelow *et al.* 2007). On pragmatic grounds, one may consider their combination for patients whose symptoms have shown only a partial response to a thorough course of either CBT or medication alone.

Conclusion

The SSRIs, all of which were initially introduced for depression, have established primacy in the treatment of most major anxiety (or anxiety-related) disorders. Their position is based on numerous placebo-controlled trials, and they are considered first-line drugs for the treatment of these disorders, followed closely by the SNRIs. There is evidence that these drugs also offer some protection against relapse. However, they are not 100% efficacious, they carry some limiting side effects, and they may require supplementation with (or substitution of) drugs from other categories. We have reviewed the main clinical trials of these other drugs and expect further progress--with both established drugs and novel categories--in the pharmacotherapy of anxiety and related disorders. Among many unexplored areas, we need to know more about the treatment of resistant and comorbid anxiety disorders, combined psychotherapy and pharmacotherapy interventions, comparative efficacy of pharmacotherapy and psychosocial treatments, and possible early interventions that may help prevent and/or alleviate the severity and chronicity of these conditions.

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CHAPTER 51

Treatment of Posttraumatic Stress Disorder

Charles B. Nemeroff, M.D., Ph.D.

Valerie Rosen, M.D.

Nicholas F. Ortiz, M.D.

After they endure a trauma, most individuals will experience a temporary increase in anxiety, dysphoria, and insomnia. For the majority, an adaptive fear-extinction process will occur over time, leading to a reduction in inappropriate reactive symptoms while still allowing improved discernment of future threats. For others, however, the ability to discern threats or inhibit fear responses elicited from neutral stimuli remains impaired following trauma and results in intrusive and distressing thoughts, avoidance of potential triggers, heightened vigilance to potential threats, and depressed mood.

Most individuals will experience a traumatic event in their lifetime. In a 2016 survey, approximately 70% of respondents reported at least one traumatic event occurring in their life. In the United States, the estimated lifetime prevalence of PTSD is 4%-8% and is higher for younger, white, female, and Native American populations (Goldstein *et al.* 2016). Among individuals with PTSD, experiencing sexual violence before age 18 years and seeing a dead body or body parts were the most common forms of trauma exposure reported (Goldstein *et al.* 2016). Alcohol and drug use disorders are highly comorbid in the PTSD population, with estimates suggesting that as many as 52% of men and 28% of women with PTSD will meet criteria for an alcohol use disorder and that 35% of men and 27% of women with PTSD will meet criteria for a drug use disorder at some point in their lives (Kessler *et al.* 1995). Similarly, depression is highly prevalent and comorbid in this population, and it is estimated that as many as half of individuals with PTSD also meet criteria for major depressive disorder (MDD) during their illness (Rosen *et al.* 2020).

Current recommendations for individuals with PTSD indicate trauma-focused psychotherapy (e.g., cognitive processing therapy, prolonged exposure, etc.) as a first-line treatment. Despite the relative success of these treatments, up to 50% of individuals with PTSD will continue to experience refractory symptoms (Bradley *et al.* 2005). The FDA approved sertraline and paroxetine for the treatment of PTSD in 1999 and 2001, respectively; however, no additional medications for PTSD have been approved to date.

Current pharmacotherapy guidelines recommend choosing a selective serotonin reuptake inhibitor (SSRI; e.g., paroxetine, sertraline, or fluoxetine) as the first-line treatment for PTSD. If PTSD symptoms are still prominent, a different SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI; e.g., venlafaxine) should be considered. If the individual has comorbid psychotic symptoms, an atypical antipsychotic such as risperidone or quetiapine should be added. If the individual has insomnia or nightmares associated with PTSD, prazosin or trazodone might be considered; however, the evidence base here is relatively weak, as described later in this chapter. Benzodiazepines and cannabis should be avoided in individuals with PTSD because they can perpetuate avoidance. Mood-stabilizing medications have demonstrated only a modest effect on PTSD symptoms at best and should only be used for patients with comorbid bipolar disorder. Several atypical antipsychotics have demonstrated meaningful effects on symptom clusters but must be weighed with consideration of their potential metabolic consequences. Newer areas of investigational therapy include repetitive transcranial magnetic stimulation (rTMS) and other neuromodulation modalities, 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy, esketamine, and psilocybin. Figure 51-1 provides a brief summary of evidence-based somatic therapies for PTSD.

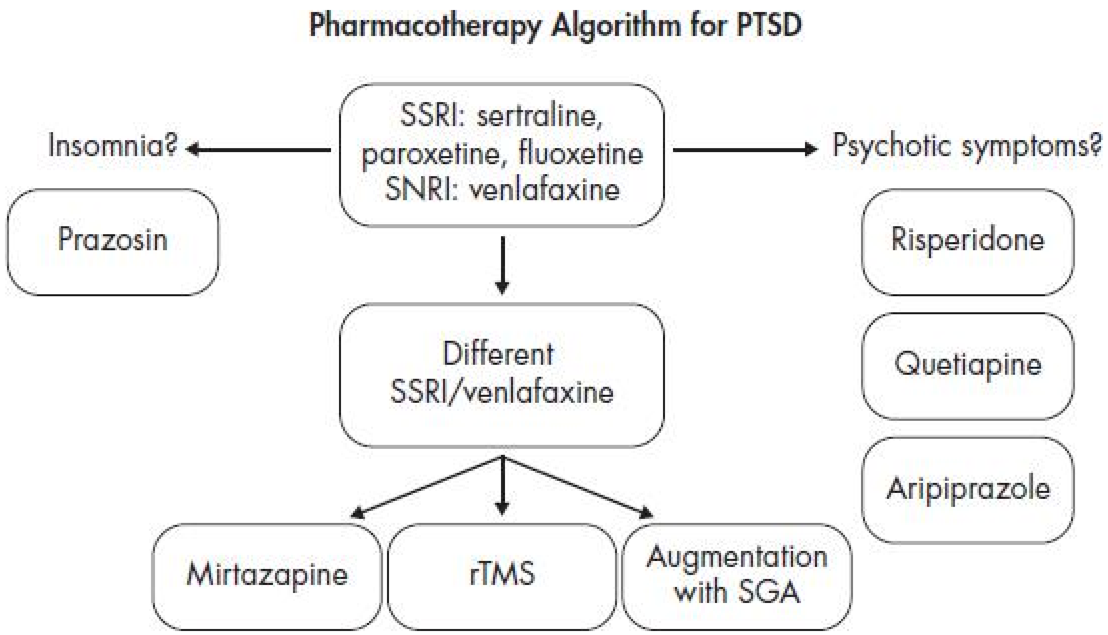
Pharmacotherapy Algorithm for PTSD
SSRI: sertraline, paroxetine, fluoxetine SNRI: venlafaxine
Insomnia?
Prazosin
Psychotic symptoms?
Risperidone
Quetiapine
Aripiprazole
Different SSRI/venlafaxine
Mirtazapine
rTMS
Augmentation with SGA

FIGURE 51-1. Pharmacotherapy algorithm for posttraumatic stress disorder.

rTMS = repetitive transcranial magnetic stimulation; SGA = second-generation antipsychotic; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Antidepressants

Selective Serotonin Reuptake Inhibitors

Only two medications are FDA approved for PTSD: sertraline and paroxetine. These medications, in addition to other SSRIs, are often used as first-line agents to treat PTSD (Mohamed and Rosenheck 2008). Current treatment guidelines from the U.S. Department of Veterans Affairs and Department of Defense (2017) and the U.K. National Institute for Health and Care Excellence (2018) all recommend SSRIs, in addition to the SNRI venlafaxine, as first-line pharmacotherapy treatments for PTSD. Overall, the estimated impact of these medications on PTSD symptoms is modest, with effect sizes (Cohen's *d*) of 0.38 for paroxetine, 0.32 for venlafaxine, 0.30 for fluoxetine, and 0.24 for sertraline (Cipriani *et al.* 2018). In two studies, investigators found no difference between SSRI treatment groups and placebo for PTSD (Hertzberg *et al.* 2000; Martenyi *et al.* 2007). Placebo-controlled studies investigating treatments for PTSD, including those in veteran populations, demonstrate very large placebo responses that often influence the detectability of a significant difference between treatment groups (Bisson *et al.* 2020; Mohamed and Rosenheck 2008). In patients with comorbidity associated with PTSD (most commonly MDD [40%-50%]), the relative effect of these medications increased (Rosen *et al.* 2020). It remains to be determined whether there is a true class effect from SSRIs or if only a select few possess clinical efficacy.

Paroxetine

Several large placebo-controlled investigations have shown paroxetine to be significantly superior to placebo for treating PTSD in diverse populations. In a 12-week placebo-controlled study involving 551 patients with PTSD, Marshall *et al.* (2001) found significantly greater reductions in PTSD symptoms (as assessed with the Clinician-Administered PTSD Scale [CAPS]), as well as in depressive symptoms, for participants receiving paroxetine compared with those receiving placebo. Side effects of paroxetine were not significantly different between groups (Marshall *et al.* 2001). In another placebo-controlled study with 307 participants (n = 156 and n = 151 in the placebo and the treatment groups, respectively), Tucker *et al.* (2001) showed significant reductions in PTSD symptoms (measured with the CAPS) and also found paroxetine to be well tolerated. A placebo-controlled trial using flexible dosing of paroxetine showed significant reductions in CAPS scores and depressive symptoms and reduced dissociation at 12 weeks of treatment (Marshall *et al.* 2007). Several open-label studies including international data from Japan and Bosnia have also shown similar reductions in PTSD symptoms in individuals treated with paroxetine (Kim *et al.* 2008; Kucukalic *et al.* 2008; Marshall *et al.* 1998).

Sertraline

Sertraline has also shown superiority compared with placebo for the treatment of PTSD in several randomized double-blind trials (Brady *et al.* 2000; Davidson *et al.* 2001; Stein *et al.* 2006). One study with 200 subjects found sertraline to be superior to placebo for reducing all symptom clusters of PTSD; however, sertraline was associated with higher rates of side effects, including diarrhea, nausea, insomnia, and fatigue (Davidson *et al.* 2001). In another study evaluating 187 participants with PTSD using flexible dosing of sertraline (50-200 mg/day), investigators reported a significantly greater reduction in the PTSD symptom clusters of hypervigilance and avoidance but not in intrusion symptoms (Brady *et al.* 2000). Insomnia was statistically more common in the treatment group than in the placebo group (Brady *et al.* 2000). Stein *et al.* (2006) conducted a double-blind, placebo-controlled study with 395 individuals with PTSD secondary to interpersonal trauma or child abuse. The authors found flexible dosing of sertraline (50-200 mg/day) to be statistically superior to placebo in the reduction of trauma symptoms (measured via CAPS scores), irrespective of the nature of the index trauma (Stein *et al.* 2006).

In other studies involving male combat veterans, investigators have not found statistical differences in PTSD symptom reduction between placebo and sertraline treatment groups. In a 12-week double-blind, placebo-controlled study in 169 male Vietnam veterans with PTSD, no difference in PTSD symptom reduction was detected between groups; 13% of sertraline-treated patients dropped out before study end as a result of side effects (Friedman *et al.* 2007). In another double-blind, placebo-controlled study evaluating 42 Israeli military veterans, investigators found no statistical difference in PTSD symptom reduction between groups after 10 weeks (Zohar *et al.* 2002). In both of these studies, the placebo response rate was substantial.

Overall, sertraline has demonstrated effectiveness in reducing PTSD symptoms in placebo-controlled trials. However, the effect size is smaller than those for other evidence-based therapies.

Fluoxetine

Although fluoxetine is not FDA approved for PTSD, several placebo-controlled trials have shown this agent to be an effective treatment option for individuals with the disorder (Connor *et al.* 1999; Martenyi and Soldatenkova 2006; Martenyi *et al.* 2002; van der Kolk *et al.* 1994, 2007). In one such study with 301 participants from war-torn regions of Israel, Europe, and South Africa, treatment with fluoxetine was associated with significant reductions in CAPS, Treatment-Outcome PTSD Scale (TOP-8), Montgomery-Asberg Depression Rating Scale (MADRS), and Hamilton Anxiety Scale (Ham-A) scores after 12 weeks. Fluoxetine was well tolerated, with a mean dosage of 57 mg/day used during the study (Martenyi *et al.* 2002). Another 5-week randomized placebo-controlled trial with 64 participants (approximately half of whom were veterans) reported significant reductions in PTSD symptoms measured by CAPS scores in nonveterans with PTSD; however, this effect was significantly diminished in the veteran subgroup (van der Kolk *et al.* 1994). Connor *et al.* (1999) conducted a double-blind, placebo-controlled trial in 53 civilian patients and found significant reductions in PTSD symptoms measured by patient and clinician rating scales at 12 weeks. Finally, another study evaluated flexible dosing of fluoxetine (20-80 mg/day) in 144 predominantly male veterans from Yugoslavia, Croatia, and Bosnia and Herzegovina (Martenyi and Soldatenkova 2006). Participants showed improvement in CAPS and TOP-8 scores after 12 weeks, and there was a significantly greater risk of relapse in the placebo group compared with the fluoxetine group at 24 weeks (Martenyi and Soldatenkova 2006).

As noted earlier, several studies have reported no statistical differences in PTSD symptom reduction with fluoxetine treatment. A recent multisite, double-blind, placebo-controlled trial of 441 predominantly female individuals assigned to a fixed dosage of fluoxetine (20 or 40 mg/day) or placebo reported no drug-related reduction in PTSD symptoms (measured with the CAPS) after 12 weeks of treatment (Martenyi *et al.* 2007). Unfortunately, there was a large placebo response rate (37%) comparable to that of fluoxetine (43% [Martenyi *et al.* 2007]). Similarly, investigators in a small placebo-controlled study of 12 male veterans with PTSD found no difference between groups in PTSD symptom reduction after 12 weeks (Hertzberg *et al.* 2000). Based on the available data, fluoxetine seems to have moderate efficacy in reducing PTSD symptoms and is well tolerated overall.

Citalopram and Escitalopram

Compared with the aforementioned SSRIs, fewer studies have examined the effect of citalopram and escitalopram on PTSD symptom reduction. In a 12-week open-label trial examining high-dosage citalopram (40 mg/day by 4 weeks) in 45 individuals with PTSD, researchers found significant reductions in CAPS scores at 3-and 6-month follow-up assessments (Qi *et al.* 2017). In another open-label trial evaluating 25 military veterans with PTSD, investigators found that fixed-dosage escitalopram (10 mg/day for 4 weeks, then 20 mg/day until study completion) resulted in significant reductions in CAPS scores in all domains, with specific improvement noted on the hyperarousal and avoidance subscales (Robert *et al.* 2006). Another open trial of citalopram in 14 adults with PTSD reported significant reductions in core symptoms of PTSD (measured via the CAPS) after 8 weeks (Seedat *et al.* 2000). However, in a comparison of sertraline ($n = 23$), citalopram ($n = 25$), and placebo ($n = 10$) for the treatment of PTSD, reductions in PTSD symptoms were observed in all three groups but were statistically significant only in the sertraline group (Tucker *et al.* 2003).

Other Antidepressants

Venlafaxine

The SNRI venlafaxine is an effective treatment for PTSD. In a large multicenter study, Davidson *et al.* (2006a) evaluated treatment responses in 538 outpatients with PTSD randomly assigned to flexibly dosed extended-release venlafaxine (mean = 225 mg/day), sertraline (mean = 151 mg/day), or placebo. At 12 weeks, the venlafaxine group demonstrated a significantly greater reduction in PTSD symptoms (measured via CAPS scores) compared with sertraline or placebo. The venlafaxine group also had the highest remission rate (30.2%; $P < 0.05$) compared with the groups treated with sertraline (24.3%) or placebo (19.6%); both venlafaxine and sertraline were well tolerated (Davidson *et al.* 2006a). Another large placebo-controlled study compared extended-release venlafaxine with placebo in adult outpatients (*N* = 329) with chronic PTSD (Davidson *et al.* 2006b). A mean dosage of extended-release venlafaxine of 221.5 mg/day was associated with significantly greater reductions in PTSD symptoms measured with CAPS scores (-51.7 for extended-release venlafaxine vs. -43.9 for placebo; *P* = 0.006) and significantly higher rates of remission (50.9% for extended-release venlafaxine vs. 37.5% for placebo; *P* = 0.01) after 24 weeks of treatment. Dropout rates did not differ between groups, and extended-release venlafaxine was well tolerated (Davidson *et al.* 2006b).

Mirtazapine

Mirtazapine is an atypical antidepressant with a unique pharmacological profile that has shown initial promise for treating individuals with PTSD. In a randomized open-label trial comparing mirtazapine and sertraline (mean dosage = 34.1 mg/day and 101.5 mg/day, respectively) in 100 Korean veterans with PTSD, researchers found that the mirtazapine-treated group had a greater reduction in CAPS scores compared with the sertraline-treated group; this difference attained statistical significance at 6 weeks. In this study, treatment with mirtazapine was associated with dry mouth and constipation in approximately 20% of individuals, whereas treatment with sertraline was associated with indigestion in 14% (Chung *et al.* 2004). Another open-label study in 13 individuals with combat-related PTSD found a CAPS reduction from a mean pretreatment score of 87.5 to 64.4 (*P* = 0.01) after 12 weeks of mirtazapine treatment (Alderman *et al.* 2009). A randomized placebo-controlled trial of 29 individuals with PTSD found improvements in Short PostTraumatic Stress Disorder Rating Interview scores after 8 weeks, and another continuation study found statistically significant reductions in scores after 24 weeks, with few dropouts related to a side-effect burden (Davidson *et al.* 2003; Kim *et al.* 2005). A 2020 placebo-controlled study with an initial 8-week double-blind phase followed by an 8-week open-label phase was conducted in 78 U.S. veterans with PTSD (Davis *et al.* 2020). The investigators found no statistically significant effect in the primary outcome measure, Structured Interview for PTSD (SIP) scores. The reduction in CAPS scores was significant in the open-label phase, and there were no significant differences in the occurrence of adverse events (Davis *et al.* 2020). Finally, a study evaluating the addition of mirtazapine to ongoing sertraline therapy for PTSD in a civilian and majority female population reported that compared with placebo, adjunctive mirtazapine treatment was associated with a greater reduction in CAPS scores and depression scales, although this difference was not statistically significant at 24 weeks (Schneier *et al.* 2015). Treatment with mirtazapine should be considered for patients with PTSD who could not tolerate or whose symptoms failed to respond to previous treatment with an SSRI (e.g., paroxetine, fluoxetine, or sertraline) or venlafaxine.

Vortioxetine

Vortioxetine is a multimodal serotonin modulator that was recently investigated in a flexible-dosage (10-20 mg/day), placebo-controlled trial in 41 individuals with PTSD. At the end of 12 weeks, vortioxetine did not separate from placebo in reducing Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) scores (Dunlop *et al.* 2021).

Duloxetine

No placebo-controlled or blinded studies investigating the effect of duloxetine in PTSD were identified in this review. One small naturalistic study of 20 male white Vietnam veterans reported that treatment with duloxetine (60-120 mg/day) was associated with significant reductions in PTSD and depressive symptoms after 8 weeks (Walderhaug *et al.* 2010).

Bupropion

In one small open-label study of 17 individuals, bupropion reduced hyperarousal symptoms of PTSD and depressive symptoms after 6 weeks (Canive *et al.* 1998). Bupropion was started at 75 mg bid and increased to 150 mg bid after 2 weeks, with a maximum allowable dosage of 200 mg bid. A larger placebo-controlled trial of 30 individuals reported no difference in the reduction of PTSD symptoms between sustained-release bupropion and placebo after 8 weeks (Becker *et al.* 2007). In this study, participants were randomly assigned (2:1) to double-blind treatment with sustained-release bupropion or placebo. Sustained-release bupropion was started at 100 mg every morning for 2 weeks and titrated up to 150 mg bid by week 4 if no significant improvement was shown (Becker *et al.* 2007).

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

In an 8-week placebo-controlled study of 62 veterans with PTSD comparing phenelzine (a monoamine oxidase inhibitor) and imipramine (a tricyclic antidepressant), both treatment groups demonstrated significant reductions in Clinical Global Impression Scale scores compared with placebo. However, reductions were greater in the phenelzine group and were even more pronounced when measured via the Impact of Event Scale (Frank *et al.* 1988). Another 8-week placebo-controlled trial comparing phenelzine, imipramine, and placebo in 60 male veterans with PTSD reported that by week 5, both treatment groups had experienced significant symptom reduction (measured using the Impact of Event Scale), with 44% improvement in the phenelzine group and 25% improvement in the imipramine group. The phenelzine group had a higher dropout rate as a result of side effects compared with the imipramine group (17% vs. 5%, respectively [Kosten *et al.* 1991]). Desipramine was not found to improve PTSD symptoms after 4 weeks in one small study of 18 war veterans (Reist *et al.* 1989). Amitriptyline was investigated in an 8-week flexible-dosage, placebo-controlled study in 46 veterans with PTSD. For individuals who completed 8 weeks of treatment ($n = 33$), there were significant reductions in scores on the Impact of Event Scale and the Hamilton Rating Scale for Depression (Ham-D); however, 64% still met criteria for PTSD (Davidson *et al.* 1990).

Evidence-Based Psychotherapy Combined With Antidepressants

A 2010 Cochrane Review evaluated four trials of combined medication and psychotherapy for PTSD. The authors concluded that there was no evidence that the combination was superior to either therapy or medication alone (Hetrick *et al.* 2010). After 10 weeks of sertraline treatment (mean dosage = 173 mg/day), patients in an augmentation strategy study were randomly assigned to either 5 additional weeks of sertraline monotherapy or sertraline plus 10 sessions of prolonged exposure over 5 weeks. Significant improvement in PTSD symptom severity stopped after 10 weeks in the medication-only group, whereas partial responders to sertraline showed further reduction in PTSD severity in the prolonged exposure augmentation group; however, the differences were not statistically significant (Rothbaum *et al.* 2006). In the Prolonged Exposure and Sertraline Trial (PROGrESS), a randomized controlled trial (RCT) of veterans with combat-related PTSD (Rauch *et al.* 2019), participants were randomly assigned to prolonged exposure therapy plus placebo, prolonged exposure therapy plus sertraline hydrochloride, or sertraline plus enhanced medication management and were followed for 24 weeks. Although all groups experienced significant reductions in PTSD symptoms, there were no significant between-group differences (Rauch *et al.* 2019). In a re-examination of PROGrESS participants who completed outcome measures after treatment, no significant differences were noted between groups in terms of residual symptoms (Tripp *et al.* 2020).

Schneier *et al.* (2012) conducted a small RCT of 37 survivors of the World Trade Center attack on September 11, 2001, with PTSD. Participants who received prolonged exposure plus controlled-release paroxetine (mean = 32.2 mg/day) versus prolonged exposure plus placebo demonstrated significantly greater improvement in PTSD symptoms, quality of life, and remission rates (8 of 19 [42.1%] with combined treatment vs. 3 of 18 [16.7%] for prolonged exposure plus placebo (Schneier *et al.* 2012). In

Poland, Popiel *et al.* (2015) conducted an RCT with 227 patients who developed PTSD after a motor vehicle accident. In terms of remission rates, prolonged exposure was superior to paroxetine and the combination of the two was not better than either alone (Popiel *et al.* 2015).

Antipsychotics

Atypical antipsychotics have pharmacological properties that may benefit individuals with PTSD, including histamine receptor antagonism, serotonin$_2$ receptor antagonism, and dopamine receptor antagonism that impact insomnia, mood dysregulation, and symptoms of hyperarousal, paranoia, and psychosis. These medications are often considered for patients with PTSD whose symptoms do not respond to initial treatment with antidepressant medications and especially for individuals with psychotic symptoms (Compean and Hamner 2019).

Risperidone

In 1994, the FDA approved risperidone for the treatment of schizophrenia. This agent has since become widely used by clinicians for a variety of psychiatric disorders, including bipolar disorder and treatment-resistant depression. Risperidone has been extensively evaluated as an augmentation agent and as a monotherapy option for PTSD.

Risperidone augmentation of current SSRI therapy has been examined in individuals with civilian and service-related PTSD. Krystal *et al.* (2011) conducted a 6-month double-blind, randomized placebo-controlled trial with 296 military veterans with service-related PTSD treated with risperidone 3 mg/day. Study participants were mostly male Vietnam veterans with severe PTSD symptoms, often with comorbid depression, and a low prevalence rate of psychotic symptoms. Individuals who received adjunctive treatment with risperidone did not demonstrate statistically significant improvement in total CAPS, global assessment (Clinical Global Impression Scale total), or quality of life (36-Item Short-Form Health Survey V) scores (Krystal *et al.* 2011).

Bartzokis *et al.* (2005) evaluated 65 male veterans with severe PTSD (CAPS score = 100, on average) in a residential treatment program for 1 month and subsequently followed them for 3 months. These participants had stable disease with a psychopharmacological regimen and were further randomly assigned to placebo or adjunctive risperidone (3 mg/day, on average). Of the 48 patients who completed the study, both groups demonstrated improvements in CAPS scores during the first month; however, only the risperidone group demonstrated a significant improvement in total CAPS scores at the study endpoint. Bartzokis *et al.* (2005) also found significant improvements in Ham-A and Positive and Negative Syndrome Scale (PANSS) scores in the adjunctive risperidone treatment group.

Rothbaum *et al.* (2008) evaluated adjunctive risperidone in a civilian PTSD population treated with sertraline. In this study, male and female participants with a CAPS score greater than 50 were treated with an open-label trial of sertraline for 8 weeks. Individuals whose symptoms did not remit (as evidenced by failure to reach a 70% reduction in CAPS scores) continued sertraline and were randomly assigned to adjunctive risperidone (2.1 mg/day, on average) or placebo. Of the 20 patients who completed Phase II of this study, there were no appreciable differences in CAPS score changes between the placebo and adjunctive risperidone groups. CAPS scores decreased by a mean 28.5 points in Phase I, followed by a placebo response that paralleled that in the adjunctive risperidone group (mean score reduction = 23.1 and 23.5 points, respectively). There were trends toward improvements in sleep quality (but not in nightmare frequency) and PANSS positive symptom subscale scores in the adjunctive risperidone group, but these results were not statistically significant.

In a study by Reich *et al.* (2004), 21 women with PTSD related to childhood physical, sexual, emotional, and verbal abuse who were in stable maintenance treatment with one antidepressant and/or one hypnotic medication were randomly assigned to adjunctive risperidone (mean dosage = 1.4 mg/day) or placebo for 8 weeks. The group receiving adjunctive risperidone (n = 9) demonstrated a significant reduction in CAPS total scores (mean = -2.74) in addition to significant reductions in CAPS hyperarousal and intrusive subscale scores.

Risperidone has also been examined in the treatment of individuals with PTSD and co-occurring psychotic symptoms. Hamner *et al.* (2003b) examined the potential efficacy of adjunctive risperidone versus placebo in 40 combat veterans with chronic PTSD with comorbid psychotic features, defined as occurrences outside flashbacks or reexperiencing episodes, with a PANSS score of 60 or higher. Participants were maintained on their previous psychotropic medications but had to have a constant medication regimen for 1 month before starting the study. The average risperidone dosage was 2.5 mg/day. All participants exhibited a significant reduction in PANSS total scores; however, the decrease in CAPS scores, present in both the risperidone and the placebo groups, did not differ statistically (Hamner *et al.* 2003b). Pivac and Kozaric-Kovacic (2006) similarly investigated risperidone as monotherapy in 26 Croatian combat veterans with PTSD who also reported hallucinations or delusions. A mean risperidone dosage of 3.6 mg/day resulted in a significant improvement in both PANSS and PTSD-Interview scores (Pivac and Kozaric-Kovacic 2006). Thus, risperidone is a rational treatment option for individuals with PTSD and co-occurring psychotic symptoms.

Quetiapine

Quetiapine is an atypical antipsychotic approved by the FDA for schizophrenia, bipolar disorder, and bipolar depression. Quetiapine is a partial agonist of the serotonin$_{1A}$ receptor and an antagonist at serotonin$_{2A}$ and dopamine$_2$ receptors, a$_1$ and a$_2$ adrenergic receptors, and histamine$_1$ receptors. The main metabolite of quetiapine, norquetiapine, is also a norepinephrine reuptake inhibitor. This pharmacological profile may afford quetiapine an advantage over other atypical antipsychotics for the treatment of PTSD.

Quetiapine has been evaluated as a monotherapy and as an adjunctive treatment to SSRIs for individuals with PTSD. Villarreal *et al.* (2016) conducted a 12-week randomized placebo-controlled trial of 80 individuals with PTSD and evaluated the effectiveness of quetiapine monotherapy using CAPS scores as the primary outcome measure. The mean quetiapine dosage used was 258 mg/day. Quetiapine-treated participants exhibited a significantly greater reduction in overall CAPS scores as well as significantly greater reductions in CAPS subscale scores for reexperiencing and hyperarousal symptoms compared with the placebo group. Patients in the treatment group were also observed to have significant reductions in PANSS, Ham-A, and Ham-D scores.

As an adjunctive treatment to SSRI therapy, quetiapine was also shown to improve CAPS subscale and PANSS scores in a small 6-week open-label trial with 20 participants (Hamner *et al.* 2003a). Ahearn *et al.* (2006) also investigated adjunctive quetiapine in 15 patients over an 8-week period (mean quetiapine dosage = 216 mg/day) and found a 40% reduction in overall CAPS scores, with significant reductions in all subscale scores.

Quetiapine has demonstrated efficacy in randomized placebo-controlled trials and thus deserves consideration as a monotherapy for individuals whose symptoms do not respond to SSRI treatment, as an adjunctive agent, and as a treatment option for individuals experiencing psychotic symptoms associated with their PTSD. Quetiapine is associated with weight gain and elevation of plasma lipids, especially triglycerides. Careful consideration should be taken before initiating quetiapine because these side effects in combination with smoking, which is prevalent in this population, can have additive effects on cardiovascular risk.

Olanzapine

Olanzapine, which shares similarities in its pharmacological profile with that of quetiapine, has also been posited to have a role in the treatment of individuals with PTSD. Several large randomized placebo-controlled studies evaluating olanzapine as a monotherapy and as an adjunctive agent have been conducted. Butterfield *et al.* (2001) performed a 10-week double-blind, placebo-controlled study with a mean olanzapine dosage of 14.1 mg/day for 15 patients with PTSD. There were no observed differences in TOP-8 scores between groups at study end (Butterfield *et al.* 2001). In contrast, Carey *et al.* (2012) conducted a similar 8-week double-blind, placebo-controlled study of olanzapine monotherapy for the treatment of PTSD. Statistically significant improvements in CAPS avoidance and numbing subscale scores, but not in overall CAPS scores, were observed.

Stein *et al.* (2002) evaluated adjunctive olanzapine treatment for SSRI-resistant combat-related PTSD. There was a statistically significantly greater reduction in CAPS scores in the olanzapine plus SSRI group compared with those treated with an SSRI alone. Not surprisingly, there was also a significant increase in weight gain (13.2 lb [6 kg]) in the olanzapine group (Stein *et al.* 2002), and the concerns described earlier in regard to hyperlipidemia and cardiovascular disease risk for quetiapine are similar, if not even greater, for olanzapine

Aripiprazole

Aripiprazole, with a unique pharmacological profile of partial agonism at the dopamine$_2$ and serotonin$_{1A}$ receptors, has demonstrated efficacy in schizophrenia, bipolar disorder, and MDD. There have been few placebo-controlled studies evaluating aripiprazole in the treatment of PTSD, and most of the current evidence is based on retrospective chart reviews. Richardson *et al.* (2011) found that of 27 military veterans with PTSD and comorbid MDD that did not respond to initial SSRI treatment and who were later prescribed aripiprazole as augmentation, 10 individuals experienced a 20% or more reduction in PTSD Checklist for DSM-IV (PCL-4) scores, with greater reductions in reexperiencing and avoidance. Mello *et al.* (2008) evaluated aripiprazole monotherapy in 32 patients with PTSD in a 16-week open-label trial with a mean aripiprazole dosage of 9.6 mg/day. The average observed reduction in CAPS scores in the aripiprazole group was 38% (from 82.7 to 51.4). At the study end, 12 of the original 32 participants had only mild PTSD symptoms (CAPS score < 39), and 6 patients achieved remission (CAPS score < 20). Side effects of aripiprazole (e.g., anxiety, psychomotor agitation, or insomnia) led six individuals to drop out of the study before 16 weeks (Mello *et al.* 2008).

Other Antipsychotics

We are unaware of any PTSD studies with data on several of the newer atypical antipsychotic drugs, including lurasidone, lumateperone, asenapine, clozapine, iloperidone, and paliperidone. We are also unaware of any clinical trials with first-generation antipsychotic agents.

Anticonvulsants

Early environmental and interpersonal stressors have been implicated in altering future sensitivity to stress and vulnerability to PTSD. This "kindling-like" phenomenon, in addition to disturbances in GABA regulation posited in PTSD, has led researchers to explore anticonvulsant medications as a potential treatment option for individuals with PTSD (Keck *et al.* 1992; Kraus 2000). Frequency of anticonvulsant use among military veterans with PTSD has been increasing over the past decade; however, this trend may reflect increased treatment of comorbid disorders associated with PTSD (Shiner *et al.* 2017).

Topiramate

There have been several controlled studies evaluating topiramate in the treatment of PTSD (Lindley *et al.* 2007; Tucker *et al.* 2007; Yeh *et al.* 2011). Two placebo-controlled studies evaluated topiramate monotherapy for civilians with PTSD (Tucker *et al.* 2007; Yeh *et al.* 2011). The mean dosages of topiramate in these studies were 76 and

103 mg/day, respectively. After 12 weeks, investigators from both studies found no significant difference in total CAPS score reduction between groups. Lindley *et al.* (2007) evaluated adjunctive topiramate versus adjunctive placebo for individuals with combat-related PTSD who were continued on a stable antidepressant regimen. The investigators similarly found no difference in CAPS score reduction between groups. The most common side effects were insomnia, somnolence, and headache (Lindley *et al.* 2007).

Divalproex/Valproate

Divalproex has been examined in civilian and veteran populations as a monotherapy and adjunctive treatment for PTSD. However, no large placebo-controlled studies have demonstrated significant PTSD symptom reduction with treatment. Davis *et al.* (Davis *et al.* (2008) conducted a placebo-controlled trial of divalproex monotherapy in 82 individuals with PTSD, with a mean divalproex dosage of 2,309 mg/day and a mean serum level of 82 mg/L. The investigators found no difference in PTSD symptom reduction between the treatment and placebo groups after 8 weeks (Davis *et al.* 2008). Another randomized placebo-controlled study of 29 individuals with PTSD of divalproex titrated to target serum levels between 50 mg/mL and 125 mg/mL found no difference in symptom reduction after 10 weeks (Hamner *et al.* 2009). Routine use of divalproex for patients without other psychiatric comorbidities such as bipolar disorder is not recommended.

Other mood stabilizers and anticonvulsants have been investigated for the treatment of PTSD. Hertzberg *et al.* (1999) conducted a small placebo-controlled study of 15 individuals with PTSD using lamotrigine monotherapy up to 500 mg/day. Symptoms were assessed by clinician ratings at each visit using the SIP and the physician-administered Duke Global Rating for PTSD scale. Several case reports reviewing the effect of lithium in individuals with PTSD reported reductions in suicidal ideation and irritability; however, improvements in overall PTSD symptoms or symptom clusters were not found (Forster *et al.* 1995; Gupta and Knapp 2013). Studies examining adjunctive pregabalin and tiagabine monotherapy have not demonstrated significant therapeutic benefit for individuals with PTSD (Baniasadi *et al.* 2014; Davidson *et al.* 2007). Baniasadi *et al.* (2014) studied 37 veteran psychiatric inpatients in Iran with chronic PTSD who had been receiving SSRIs (citalopram 20-40 mg/day or sertraline 50-200 mg/day) and sodium valproate (1,000-1,800 mg/day) for a minimum duration of 1 month. Pregabalin (75 mg/day in week 1, 75 mg bid in week 2, and titrated to 150 mg bid for the remaining weeks 3-6) was added to the this medication regimen for the active-treatment group (n = 18) compared with a placebo-added control group (n = 19). PCL-4-Military scores were significantly reduced in both groups, and pregabalin was significantly more effective compared with placebo (P = 0.045), although not robustly so. No significant between-group differences in Ham-D and Ham-A scores were found (Baniasadi *et al.* 2014). Longer-term studies are needed to assess whether adjunctive pregabalin may be effective for PTSD. Gabapentin has demonstrated limited effectiveness as an adjunctive treatment for PTSD; however, no studies have shown gabapentin monotherapy to be effective. A retrospective study of 30 patients with PTSD treated with adjunctive gabapentin (300-3,600 mg/day) showed moderate improvements in nightmare frequency and sleep duration (Hamner *et al.* 2001). Two placebo-controlled studies evaluated gabapentin monotherapy in addition to an

active comparator, propranolol or pregabalin, as a preventive treatment for the development of PTSD and depressive symptoms following a traumatic event. Both studies reported no difference in symptom development between treatment groups and the placebo group (Fowler *et al.* 2012; Stein *et al.* 2007).

Anticonvulsants should not be used as a first-line treatment for individuals with PTSD and should only be considered for individuals with comorbid bipolar disorder who are unable to tolerate SSRI and/or SNRI medications or atypical antipsychotics.

Benzodiazepines

Benzodiazepines are effective anxiolytics for several anxiety disorders. Guina *et al.* (2015) performed a systematic review and meta-analysis of benzodiazepines for PTSD including four RCTs. Despite a few studies showing short-term improvement in sleep and anxiety, the overall evidence was in agreement with several PTSD treatment guidelines in concluding that benzodiazepines at best are ineffective for core PTSD symptoms and at worst may increase the risk of developing PTSD or may worsen PTSD symptoms (Guina *et al.* 2015). A large retrospective study of more than 200,000 veterans with PTSD treated in the VA system reported that those treated with benzodiazepines had higher rates of health care utilization, including emergency room visits, hospitalizations, and outpatient care, in addition to higher rates of suicidality and suicide attempts than those not prescribed benzodiazepines (Deka *et al.* 2018).

Risks of benzodiazepines in this population include the potential to develop dependency, withdrawal, and tolerance, especially in light of the frequency of comorbid substance use disorders in patients with PTSD. In first-line trauma-focused psychotherapies, benzodiazepines interfere with a patient's ability to feel and process their emotions and collude with the tendency to avoid; therefore, they are relatively contraindicated during psychotherapy for PTSD (Resick *et al.* 2017). Long-and short-term risks such as irritability or paradoxical activation, cognitive impairment, and risk of falls in elderly individuals, combined with a lack of efficacy and their potential to worsen symptoms, support the conclusion that the risks of benzodiazepines typically outweigh short-term benefits in the treatment of PTSD.

Prazosin

Prazosin is an antihypertensive and a_1-adrenergic receptor antagonist that crosses the blood-brain barrier and counteracts the potentially increased noradrenergic outflow that may contribute to nightmares in rapid eye movement sleep (Raskind 2020). Studies examining prazosin for PTSD have shown conflicting results. Raskind *et al.* (2016) used standing systolic blood pressure as an indicator of activity regulated by a_{1A}-adrenergic receptors on peripheral arteries to predict the effect of prazosin in active-duty soldiers after combat. For each 10-mmHg increase in baseline standing systolic blood pressure, there was a resultant 14-point decrease in the CAPS total score only for those who received prazosin (Raskind *et al.* 2016). In a more recent well-powered multicenter RCT, Raskind *et al.* (2018) demonstrated no significant difference between prazosin and placebo in 304 VA patients. Hypotheses for the negative results in this second trial included the following (Ressler 2018): First, patients with less severe PTSD were enrolled (psychosocial instability was an exclusion criterion). Second, sleep apnea was not an exclusion criterion and may have masked prazosin's effects. Third, those taking trazodone (a partial a_1-adrenergic antagonist) with benefit did not enroll (trazodone use was an exclusion criterion). Finally, other large VA trials have shown negative effects when the trial drug is already being used by many patients (i.e., successful responders might not have been eligible for the study) (Ressler 2018). In a systematic review and meta-analysis of six RCTs including the aforementioned Raskind *et al.* (2018) trial, a pooled analysis of 429 patients showed that prazosin produced significantly greater improvement in nightmares, sleep quality, and overall PTSD scores compared with placebo (Reist *et al.* 2021). In another meta-analysis of eight RCTs with prazosin that also included the Raskind *et al.* (2018) trial, treatment with prazosin produced significantly greater improvement in nightmares, but not in overall PTSD symptoms or sleep quality, compared with placebo (Zhang *et al.* 2020).

Imagery rehearsal therapy has shown large effect sizes in reducing nightmare frequency and distress (van Schagen *et al.* 2015). A meta-analysis of RCTs using imagery rehearsal therapy versus prazosin reported that prazosin effect sizes were larger but not significantly so (Yucel *et al.* 2020). Performing well in comparison with another evidence-based treatment for nightmares lends credence to the fact that for many, prazosin is effective in reducing trauma nightmares. It can be inferred that at the very least, a subset of patients with prominent a_1-adrenergic-mediated hyperarousal may benefit more from prazosin (Raskind 2020; Ressler 2018). An advantage is its general tolerability; the side effects of prazosin that differed significantly from placebo were dry mouth (Zhang *et al.* 2020), dizziness, lightheadedness, and urinary incontinence (Raskind *et al.* 2018). Symptomatic hypotension was rare but should be a consideration, especially for individuals with a history of hypotension or other cardiac issues at baseline and those at risk for falls.

Psychedelic Drug-Assisted Psychotherapy

Psychedelic drug-assisted psychotherapy is designed to utilize psychedelics as adjuncts to psychotherapy to enhance patients' ability to emotionally and cognitively process trauma via pharmacological reduction of fear and arousal, increase in trust, and assistance with memory consolidation (Krediet *et al.* 2020).

3,4-Methylenedioxymethamphetamine

MDMA promotes the release of serotonin, dopamine, and norepinephrine (Clemens *et al.* 2007) and is categorized as an entactogen because it increases comfort with expression of feelings (Bahji *et al.* 2020). MDMA increases oxytocin release, which is linked to the prosocial effects of MDMA (Dumont *et al.* 2009) and is postulated to improve the therapeutic alliance in psychotherapy (Mithoefer *et al.* 2016). Proposed mechanisms for the effects of MDMA-assisted psychotherapy in PTSD improvement include reduced cerebral blood flow to the amygdala, increased connectivity between the hippocampus and amygdala, facilitation of synaptic plasticity via cholinergic signaling, and activation of brain-derived neurotrophic factor (BDNF) signaling that induces changes in memory (Feduccia and Mithoefer 2018). MDMA may enhance memory reconsolidation and processing in addition to fear extinction (Feduccia and Mithoefer 2018).

In terms of its safety profile, changes in postreceptor signaling suggest that chronic MDMA use may lead to chronic reductions in serotonin signaling (Benningfield and Cowan 2013; Parrott 2014). Chronic users may also experience hyponatremia, memory deficits, persistent sleep abnormalities, depression, and increased aggression, and pregnant women who misuse MDMA have been reported to have children with lower-quality motor scores (Parrott 2014). Much of the safety data just described are derived from retrospective reports with unclear confounders, such as polydrug use disorders (Mithoefer *et al.* 2016). Side effects of acute MDMA intoxication include difficulty concentrating, confusion, blurred vision, sweating, and intensification of negative emotional states (Parrott 2014). If mood is enhanced while taking MDMA and this results in a post-MDMA depressive effect (even if transient), there are questions of inducing drug-seeking behavior to "feel good" (Parrott 2014). Others argue that MDMA is safe if taken a limited number of times, in safe dosages, and with supervised administration and that brief use is not a fair comparison to chronic use of the drug (Feduccia *et al.* 2019; Morgan 2020). Side effects that occurred at a frequency at least twice that in the control group in Phase II trials with MDMA-assisted therapy included diarrhea, difficulty concentrating, dizziness, heavy legs, impaired gait or balance, jaw clenching or tight jaw, nausea, lack of appetite, paresthesia, perspiration, sensitivity to cold, thirst, nystagmus, and weakness (Feduccia *et al.* 2019).

In MDMA-assisted therapy, MDMA is not the treatment per se but rather a means to enhance participation in the primary treatment modality, psychotherapy (Morgan 2020). In Phase II trials, participants received the following: three preparatory psychotherapy sessions; two to three blinded 8-hour psychotherapy sessions with MDMA (75-125 mg) or a comparator or placebo (0-40 mg MDMA); and three 90-minute nondrug psychotherapy visits following each MDMA-assisted session (Feduccia *et al.* 2019). In a systematic review and meta-analysis of five Phase II trials conducted between 2004 and 2013 in the United States, Spain, and Switzerland with 106 participants, MDMA-assisted therapy demonstrated a large effect size in treatment-refractory PTSD, with improvements in remission rates and a significant reduction in PTSD symptoms, and with gains maintained from 2 to 74 months (Bahji *et al.* 2020). Data pooled over all six Phase II trials showed statistical significance over the control, with a between-group Cohen's *d* (effect size) of 0.9, compared with effect sizes for prior Phase II trials of 0.45-0.56 for paroxetine and 0.31-0.37 for sertraline. Feduccia *et al.* (2019) concluded that MDMA-assisted psychotherapy was superior to paroxetine and sertraline in terms of having greater safety and efficacy and lower dropout rates, leading the FDA to grant MDMA-assisted psychotherapy a breakthrough therapy designation in 2017.

A randomized double-blind, placebo-controlled Phase III study was conducted at 11 U.S., 2 Canadian, and 2 Israeli sites, with a total of 42 and 37 participants in the MDMA and placebo groups, respectively, who completed treatment. Manualized therapy with MDMA or with placebo consisted of three preparatory and nine integrative therapy sessions. The MDMA dose ranged from 80 to 180 mg (compared with 75-125 mg in Phase II trials). The experimental sessions consisted of an initial dose and an optional supplemental half-dose 1.5 to 2.5 hours after the initial dose; session 1 included 80 + 40 mg, and sessions 2 and 3 included 120 + 60 mg. Six participants declined the supplemental dose or chose not to escalate the dose. A history of substance use disorder, severe childhood trauma, or dissociative PTSD subtype did not affect treatment outcomes. MDMA produced significantly greater reductions in CAPS-5 scores compared with placebo ($P < 0.0001$, $d = 0.91$) and significantly greater decreases in Sheehan Disability Scale scores ($P < 0.0116$, $d = 0.43$). For treatment completers, the mean (+- SD) change in CAPS-5 scores was [?]24.4 +- 11.6 in the MDMA group and [?]13.9 +- 11.5 in the placebo group. Two months after the last session, 67% of the MDMA group no longer met criteria for PTSD, compared with 32% of the control group. Reported adverse effects from MDMA included muscle tightness, decreased appetite, nausea, hyperhidrosis, feeling cold, and a transient increase in blood pressure and heart rate. MDMA did not induce adverse events of suicidality, abuse potential, or QT prolongation; however, longer-term follow-up is necessary to fully exclude these and other potential side effects (Mitchell *et al.* 2021).

A remaining source of contention is that most of the MDMA research has been conducted by one group of researchers, the Multidisciplinary Association for Psychedelic Studies (Morgan 2020). Some feel that the evidence is insufficient to recommend MDMA-assisted psychotherapy over more conventional treatments (Bahji *et al.* 2020; Reiff *et al.* 2020); however, the initial Phase III results are promising.

Psilocybin

Psilocybin (phosphoryloxy-*N*,*N*-dimethyltryptamine), derived from mushrooms or in synthetic form, is metabolized to psilocin, which is a serotonin transporter inhibitor and a serotonin$_{2A}$ receptor partial agonist that also binds to serotonin$_{2C}$, serotonin$_{1A}$, and serotonin$_{1B}$ receptors (Rickli *et al.* 2016). Psilocybin received an FDA breakthrough therapy designation for use in depression (Krediet *et al.* 2020) but not for PTSD. For the treatment of depression, a postulated mechanism of action is through the default mode network and frontal brain connectivity changes; psilocybin may cause system-level alterations that improve mood (Johnson *et al.* 2019). Psilocybin has been shown to enhance fear extinction in mice (Catlow *et al.*

2013) and reduce amygdala reactivity in humans (Kraehenmann *et al.* 2015), both of which could prove beneficial in PTSD treatment. Data from animal studies can be interpreted to show that psilocybin may create episodes of behavioral flexibility that enhance learning of new psychotherapeutic skills. Hypothetically, altered sensory perception and integration of details may also allow for reduced rigidity or ruminative thinking (De Gregorio *et al.* 2021). In terms of suicidal ideation (often present in PTSD), data show that psilocybin increases mystical or spiritual experiences (Griffiths *et al.* 2018), which could confer protection from suicide from a religious or spiritual perspective (Nobile *et al.* 2020).

Psilocybin-assisted psychotherapy involves at least one predrug psychotherapy session, nondirected drug-assisted sessions that include multiple check-ins, and at least one postdrug session (Carhart-Harris *et al.* 2016; Griffiths *et al.* 2016; Kaelen *et al.* 2018). In the dose range of 10-25 mg (Krediet *et al.* 2020), effects have been shown to last 3-6 hours (Passie *et al.* 2002). Side effects include mild elevations in blood pressure and heart rate, transient vomiting or nausea, stressful emotional experiences (e.g., confusion and anxiety), and alterations in perception (e.g., visual or auditory

hallucinations); psilocybin is not deemed to cause serious side effects or dependence in small, supervised doses (Johnson *et al.* 2018). Although current RCTs are lacking, past unstructured research with smaller samples demonstrated positive effects in survivors of trauma (Krediet *et al.* 2020), and current studies are under way.

Cannabis

D-9-Tetrahydrocannabinol (THC) is one of the major psychoactive ingredients in marijuana (Hindocha *et al.* 2020), and cannabidiol (CBD) is a nonpsychotomimetic component (Pisanti *et al.* 2017). The endogenous endocannabinoid system is composed of cannabinoid receptors CB_1 and CB_2. CB_1 receptors are expressed in the amygdala, hippocampus, and prefrontal cortex; CB_2 receptors are located primarily in the periphery but have been shown to be present in the aforementioned brain areas as well (Orsolini *et al.* 2019). CBD imparts lower CB_1 and CB_2 receptor affinity than THC (Pisanti *et al.* 2017). The endogenous endocannabinoid system also includes endogenous cannabinoids such as *N*-arachidonoyl ethanolamine (anandamide) and 2-arachidonoylglycerol (Hindocha *et al.* 2020). An anandamide-degrading enzyme, fatty acid amide hydrolase (FAAH), has been hypothesized to be a target for novel PTSD medications. In an RCT of healthy male participants, JNJ-42165279, a novel drug that inhibits FAAH, was administered for 4 days (Paulus *et al.* 2021). The results showed that the drug reduced activation in the amygdala, anterior cingulate, and insula during a face recognition task; it also increased activation in the anterior cingulate, bilateral anterior insula, and right inferior frontal cortex during anticipation of an aversive interoceptive event but did not affect fear conditioning or extinction (Paulus *et al.* 2021).

A recent systematic review examined several types of cannabinoids for PTSD treatment (Orsolini *et al.* 2019). Results for medical cannabis use were conflicting, with some showing a reduction in PTSD symptoms (Bonn-Miller *et al.* 2014; Greer *et al.* 2014) and others showing worsening PTSD symptomatology, violent behavior, and substance use (Wilkinson *et al.* 2015). In an open-label pilot study of 10 patients who received orally absorbable THC (5 mg bid) as an adjunct to other medications, there was a statistically significant reduction in PTSD severity, a decrease in nightmare frequency, and improvement in sleep quality (Roitman *et al.* 2014).

A small retrospective chart review case series of 11 patients demonstrated that oral CBD reduced scores on the PTSD Checklist for DSM-5 (PCL-5) by 28% (from 51 to 37) after 8 weeks of treatment with no side effects. Study limitations included confounders such as allowing for other concurrent PTSD treatments (e.g., therapy, medication), inconsistent dosing of CBD, and failure to exclude patients who were using cannabis on their own (Elms *et al.* 2019).

Nabilone, a synthetic THC analog and CB_1 receptor agonist that is FDA approved for treatment of chemotherapy-induced nausea and vomiting, was examined in a placebo-controlled double-blind crossover study in Canadian military members with PTSD. This drug reduced CAPS scores for recurring and distressing dreams (Jetly *et al.* 2015). In a retrospective chart review study with 104 participants with PTSD in a correctional facility, those given nabilone showed a decrease in PCL-4 scores and nightmares. Confounders included that most participants had severe mental illness, many had cannabis use disorder, and only patient-rated outcomes were used (Cameron *et al.* 2014; Hindocha *et al.* 2020). In an open-label clinical trial of 47 patients with PTSD, nabilone reduced nightmares in 72% of participants (Fraser 2009).

A 2020 systematic review of cannabinoids for PTSD covering studies up to December 2018 found only one RCT and nine other studies that showed promise for this treatment modality. Small sample sizes and low-quality ratings were limiting, and the investigators concluded that there was insufficient evidence to support cannabinoid use for routine treatment of PTSD (Hindocha *et al.* 2020).

Common side effects of cannabis use in the abovementioned studies included dry mouth, headaches, feeling "stoned," sedation, lightheadedness or dizziness, and stomach irritation (Cameron *et al.* 2014; Elms *et al.* 2019; Fraser 2009; Roitman *et al.* 2014). A more significant but less common side effect is psychosis, which is more frequent in those with a genetic predisposition (Cameron *et al.* 2014).

The potential for a substance use disorder is a valid concern, especially in regard to long-term cannabis use. A longitudinal observational study of 361 veterans deployed after September 11, 2001, found no evidence of decreased intrusive symptoms or PTSD remission in long-term cannabis users and concluded that long-term use may be associated with a worsening of intrusive symptoms (Metrik *et al.* 2020). In a nationwide longitudinal VA study of veterans with opioid use disorder and PTSD, cannabis use was not associated with a substantial reduction in opioid use, days of substance use, abstinence, or severity of PTSD symptoms (De Aquino *et al.* 2020). The potential for a cannabis use disorder remains an unanswered question; however, results from an earlier study showed that individuals with PTSD were more likely to use cannabis as a coping mechanism, with the perception, whether valid or not, that it could help reduce their PTSD symptoms (Cougle *et al.* 2011).

Ketamine

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. Its mechanism of action in terms of antidepressant effects and impact on PTSD is not yet fully elucidated (Stein and Simon 2021). Impaired synaptic connectivity may detrimentally affect neuroplasticity in PTSD and is postulated to be connected to glutamate dysregulation via processes including reduced signaling via BDNF. In rats, ketamine given after stress normalized hippocampal decreased BDNF concentrations (Zhang *et al.* 2015). Ketamine may theoretically improve PTSD symptoms by stimulating glutamate release and increasing BDNF release and activation of the Akt/molecular target of rapamycin pathway, ultimately resulting in the creation of new dendritic spines (Krystal *et al.* 2017). In a rodent study, extinction exposure and ketamine increased levels of molecular target of rapamycin complex 1 (mTORC1) and c-Fos (a marker of neuronal activity) in the medial prefrontal cortex, supporting the above hypothesis in terms of enhancing fear extinction (Girgenti *et al.* 2017). Alternatively, ketamine may block extrasynaptic NMDA glutamate receptors to increase BDNF (Krystal *et al.* 2017). There is now substantial evidence from both preclinical and clinical investigations demonstrating that ketamine acts in part on endogenous opioid systems. Seminal studies by Williams *et al.* (2018) conclusively showed that the m opioid receptor antagonist naltrexone completely abolishes the antidepressant and antisuicide effects of ketamine. Several laboratory animal studies support these findings. Ketamine may act as a m opioid agonist like other opioid analgesics and/or may increase the release of endogenous opioids such as b-endorphin.

Ketamine is a dissociative anesthetic that is also a drug of abuse. The recent FDA approval of intranasal use of esketamine for treatment-resistant depression sparked investigation of its use in comorbid depression and PTSD and in PTSD alone. Several single case reports showed efficacy in reducing PTSD symptom severity; however, symptoms returned 2 weeks after ketamine treatment (D'Andrea and Sewell 2013; Donoghue *et al.* 2015; Womble 2013).

Earlier studies were discordant, with some evidence that ketamine may worsen PTSD. A retrospective study of motor vehicle accident survivors who received a peritraumatic dose of racemic ketamine, esketamine, or opioids en route to the hospital found that esketamine strongly increased acute symptoms of dissociation, reexperiencing, and avoidance, whereas racemic ketamine mildly increased them. The esketamine group also showed significantly more severe PTSD symptoms compared with the other two groups 1 year after trauma (Schonenberg *et al.* 2005). Combat veterans with PTSD (*n* = 147) who received ketamine perioperatively for burn injuries had a lower prevalence of PTSD than those who did not receive ketamine (McGhee *et al.* 2008). In a follow-up study with a larger sample (*n* = 289), the two groups did not show any difference in syndromal PTSD rates (McGhee *et al.* 2014). Subsequent studies have been more positive. Oral ketamine was shown to reduce hospital stay duration by 70% in a study of 37 patients with comorbid depression and PTSD (Hartberg *et al.* 2018). In an RCT (*n* = 41), single-dose intravenous ketamine was superior to the active control (midazolam) in reducing PTSD and depressive symptoms in an initial study with 2-week follow-up (Feder *et al.* 2014). In a subsequent RCT (*n* = 30), six intravenous infusions of either ketamine or the active control (midazolam) were given over 2 consecutive weeks. Based on improvement in scores on the CAPS-5 and MADRS, 20% of the control group responded to treatment (liberally defined as > 30% symptom improvement after 2 weeks of initial infusion), specifically in the clusters of avoidance, intrusions, and negative alterations in mood and cognitions, compared with 67% of the ketamine group. For responders, 27.5 days was the median time to loss of treatment response (Feder *et al.* 2021). This result was consistent with findings in an earlier open-label repeated ketamine infusion study of six infusions over a 12-day period. Investigators demonstrated a PTSD remission rate of 80% and a treatment-resistant depression response rate of 93%, with symptom relapse on days 41 and 20 after treatment for PTSD and depression, respectively (Albott *et al.* 2018).

In terms of ketamine's side-effect and safety profile, one participant in the study by Feder *et al.* (2014) dropped out because of a lack of improvement and possible worsening of PTSD symptoms after two ketamine infusions, and another had hypertension that required treatment. Other minor side effects included transient dissociative symptoms, blurred vision, dizziness, nausea, vomiting, headache, and fatigue. Patients with a psychotic or substance use disorder were excluded; therefore, ketamine's potential for abuse or exacerbation of psychosis was not examined (Feder *et al.* 2021). A systematic review of ketamine use for depression reported a similar side-effect profile, and the authors noted that more research is needed to assess long-term effects, especially when given in repeated dosing, as repeated use of ketamine in anesthesia or chronic pain, and/or recreationally has been associated with hepatotoxicity, urotoxicity, and deficits in cognition, including short-and long-term memory (Short *et al.* 2018). Questions remain regarding long-term safety, effectiveness, tolerability, and whether combining ketamine with evidence-based psychotherapy may help sustain a treatment response.

Nitrous Oxide

Nitrous oxide, an inhaled anesthetic, is a noncompetitive NMDA receptor antagonist that mechanistically may work in a manner similar to ketamine for PTSD. In a case

report series of three veterans with PTSD, nitrous oxide was delivered via face mask in a single 1-hour treatment of anesthetic inhalation of 50% nitrous oxide and 50% oxygen. CAPS-5 scores were obtained at baseline and 1 week after drug administration, with response defined as a reduction of 12 points at day 7. Two of the three patients met this response criterion, with a reduction of 16 and 17 points in CAPS-5 scores at day 7. On the Impact of Events Scale-Revised version, the two responders showed almost complete resolution of symptoms on day 1: one had sustained symptom improvement, and the other had a gradual return to baseline by day 7. Side effects included nausea, poor concentration, and vomiting (Varias *et al.* 2020).

Nitrous oxide completely suppressed stress-enhanced fear learning in a rodent study (Rau *et al.* 2009), suggesting that it may be useful in preventing PTSD. Nitrous oxide was used to prevent memory consolidation in 52 healthy participants exposed to violent film clips who were given either 50% nitrous oxide or oxygen for 30 minutes (Das *et al.* 2016).

Negative intrusions were not statistically different between groups; however, the nitrous oxide group showed a markedly faster reduction in intrusion frequency over 7 days. Similar between-group measurements of heart rate variability and sleep point against these variables influencing the results. The nitrous oxide group experienced more dissociation, which warrants concern for possible exacerbation of PTSD (Das *et al.* 2016). This study of laboratory-induced "trauma" suggests that nitrous oxide may speed the reduction of intrusions after trauma, but these findings must be replicated in larger PTSD samples.

D-Cycloserine

D-Cycloserine is a partial NMDA agonist and has been shown to improve fear extinction in animals (Hoskins *et al.* 2021). Of two studies assessing D-cycloserine as an add-on therapy for PTSD, one demonstrated no difference from placebo (Heresco-Levy *et al.* 2002) and one showed a significant decrease only in symptom intensity in the first of two 4-week intervention periods (Attari *et al.* 2014). In a recent meta-analysis examining D-cycloserine as an add-on to psychotherapy, the following four studies used different doses and time points for administration and reported conflicting results (Hoskins *et al.* 2021). Among women who had experienced sexual abuse, D-cycloserine did not differ from placebo when administered 1 hour before face-to-face prolonged exposure sessions (de Kleine *et al.* 2012). In a small group of survivors of the World Trade Center attack on September 11, 2001, remission rates were higher for D-cycloserine plus cognitive-behavioral therapy (CBT) via virtual reality exposure (VRE) than for placebo plus CBT via VRE (Difede *et al.* 2014). In a small study of combat veterans, the placebo plus exposure group had greater symptom reduction than the D-cycloserine plus exposure group, and three of the D-cycloserine-treated participants experienced worsening of their PTSD symptoms (Litz *et al.* 2012). A randomized trial of veterans comparing D-cycloserine plus VRE, alprazolam plus VRE, or placebo plus VRE showed no significant differences among the three groups in the primary outcome measures (i.e., CAPS and PTSD symptom scale scores). However, salivary cortisol and startle responses were significantly lower in the D-cycloserine group, suggesting that reduced reactivity in this group may have been related to enhanced extinction learning that was associated with the D-cycloserine group only (Rothbaum *et al.* 2014). In addition, a pediatric study reported that D-cycloserine plus manualized youth CBT exposure therapy was not significantly different from placebo plus the same exposure therapy (Scheeringa and Weems 2014). Side effects in these studies were minor, did not differ significantly from placebo, and included nausea, headache, drowsiness, irritability (in pediatric patients), dizziness, and dry mouth (Baker *et al.* 2018). Currently, evidence is lacking to recommend D-cycloserine for the treatment of PTSD.

Neuromodulation

Electroconvulsive Therapy

Modern electroconvulsive therapy (ECT), which utilizes brief and ultrabrief pulses of rectangular rather than sine wave current, has substantially reduced the severity of cognitive side effects in comparison with older versions of this therapy while maintaining significant effectiveness for various mental disorders such as depression. ECT has also been shown to increase hippocampal neurogenesis and cortical volume (Ousdal *et al.* 2020). The effects of ECT on memory consolidation may be of potential benefit for individuals with PTSD, as previous research has shown the potential sensitivity of reactivated emotional memories to disruption following ECT treatments in individuals with depression (Kroes *et al.* 2014).

Multiple retrospective analyses have examined the impact of ECT in patients with comorbid MDD and PTSD (Ahmadi *et al.* 2016; Kaster *et al.* 2018; Watts 2007) and have demonstrated reductions in depressive and PTSD symptoms. In the largest retrospective case-control study examining the efficacy of ECT in treating PTSD and depression comorbidity (3,485 participants with comorbid MDD and PTSD [of whom 92 were treated with ECT and 3,393 were not treated with ECT] and 18,679 without MDD or

PTSD), ECT was associated with a reduction in depressive and PTSD symptoms; PTSD symptoms improved independent of depressive symptoms (Ahmadi *et al.* 2016). This study also reported that individuals with PTSD who received ECT treatment exhibited reductions in suicidality as well as cardiovascular and all-cause mortality (Ahmadi *et al.* 2016). Margoob *et al.* (2010) conducted the only identified open-label prospective clinical trial to date for adults with PTSD symptoms that failed to respond to at least four different antidepressants along with 12 sessions of CBT. Of the 20 individuals who began the fixed course of six bilateral ECT treatments, all but 3 completed the study. At the study end, the mean CAPS score had decreased from 91.7 to 55.1 and depressive symptoms assessed using the MADRS had decreased from 23.5 to 10.1 (Margoob *et al.* 2010). The evidence supporting ECT treatment for individuals with PTSD is still limited; however, for appropriate patients with comorbid depressive symptoms or severe and refractory PTSD symptoms, ECT should be considered as an effective alternative treatment option.

Repetitive Transcranial Magnetic Stimulation

rTMS is FDA approved for major depressive disorder and has been increasingly investigated for the treatment of PTSD. In rTMS, a magnetic field is created that safely passes through the scalp and skull and alters the excitability and activity of cortical and, to a lesser extent, subcortical structures--often the dorsolateral prefrontal cortex (dlPFC) or medial prefrontal cortex. Although studies have investigated left-sided and bilateral treatments (Boggio *et al.* 2010; Carpenter *et al.* 2018; Philip *et al.* 2016, 2018), the majority of supporting evidence indicates the likelihood that right-sided treatment is superior (Kan *et al.* 2020). Low-and high-frequency (1 and 15-20 Hz) stimulation has opposing effects on neural excitability and blood flow. Low-frequency stimulation decreases excitability, whereas high-frequency stimulation increases it. However, both forms of stimulation have demonstrated effectiveness in treating core symptoms of PTSD, indicating that improvement may be independent of stimulation intensity (Kozel *et al.* 2019).

Evidence supports the effectiveness of rTMS as monotherapy and as an adjunctive treatment for PTSD. Cohen *et al.* (2004) conducted a study in 24 patients randomly assigned to 2 weeks of 10 daily treatments (10 Hz, 1 Hz, or sham) over the left dlPFC. The authors found that individuals receiving excitatory stimulation had significant reductions in PTSD and anxiety symptoms measured via the CAPS and Ham-A, respectively (Cohen *et al.* 2004). Another sham-controlled crossover study of nine individuals evaluated a combination of exposure therapy and 1-Hz rTMS over the right dlPFC, and the investigators observed significant improvements in hyperarousal symptoms measured via CAPS scores (Osuch *et al.* 2009).

Intermittent theta-burst stimulation (iTBS) is a patterned form of rTMS that has also demonstrated effectiveness in the treatment of PTSD. iTBS utilizes short bursts of high-frequency (50-Hz) stimulation repeated at 5-Hz intervals that deliver stimulation pulses more quickly, allowing a reduction in overall treatment time (5 vs. 30 minutes) compared with traditional rTMS. In a recent study, Philip *et al.* (2019) randomly assigned 50 veterans with PTSD to 10 days of sham-controlled iTBS followed by 10 unblinded treatments. At 2 weeks, active iTBS treatment was associated with significant improvement in Social and Occupational Functioning Assessment Scale scores (Philip *et al.* 2019).

Transcranial Direct Current Stimulation

In transcranial direct current stimulation (tDCS), a small current (usually 2 mA) is run through the brain via electrodes, leading to subthreshold shifts in neuronal resting membrane potential, with anodal orientation increasing cortical excitability and cathodal orientation decreasing it (Priori *et al.* 2009). Previous investigations have demonstrated moderate effectiveness for tDCS in treating depression (Bennabi and Haffen 2018; Brunoni *et al.* 2013), although this modality is not FDA approved. Ahmadizadeh *et al.* (2019) conducted a tDCS sham-controlled trial for individuals with PTSD (n = 44) and found improvements in hyperarousal and cognitive symptoms as well as in depressive symptoms after 10 sessions of bilateral tDCS over the dlPFC. Another sham-controlled investigation incorporating tDCS as an adjunctive treatment to VRE therapy reported significantly greater reductions in hyperarousal symptoms in the treatment group compared with the control group (van't Wout-Frank *et al.* 2019). Although the generalizability of these findings is limited by small sample sizes, these studies offer a framework for the feasibility and potential therapeutic benefit of tDCS treatments in the future.

Stellate Ganglion Block

A stellate ganglion block (SGB) involves an injection of a local anesthetic, typically under ultrasound or fluoroscopic guidance, between C6 and C7 into the stellate ganglion nerve bundle. SGB inhibits sympathetic nerve impulses and has been used to successfully treat disorders such as complex regional pain syndrome, hot flashes, migraines, facial pain, and upper-extremity pain (Peterson *et al.* 2017). When SGB was used to treat these conditions, some improvements in psychological symptoms were observed, leading researchers to test its effectiveness in PTSD. This temporary sympathetic block may help reduce fight-or-flight responses, which are tied to hyperarousal in PTSD. It is postulated that when severe, hyperarousal symptoms may reduce the efficacy of treatment (McCurry *et al.* 2020; Stein *et al.* 2012). Brain areas associated with hyperarousal in PTSD, including the hypothalamus, amygdala, and insular cortex, are all accessible via the stellate ganglion afferents (Westerhaus and Loewy 2001).

A case series of 166 patients receiving SGBs showed that 70% had clinically significant improvement (a reduction of at least 10 points in PCL-4-Military scores), which persisted for 3-6 months (Mulvaney *et al.* 2014). In anecdotal clinical case reports of SGBs administered to 24 patients after a year of psychotherapy and medication management, 75% showed meaningful improvement in PTSD scores (Lipov and Ritchie 2015). The initial RCT for SGB for PTSD showed that the range of improvement in PTSD symptoms was not statistically different from saline placebo (Hanling *et al.* 2016). There were many methodological limitations, including 1) using a lesser-known anesthetic and dose, 2) not injecting in the same location on each participant, 3) not utilizing accepted outcome measures for PTSD, and 4) using a secondary gain variable because many participants were in the midst of compensation evaluations for PTSD (Peterson *et al.* 2017). In a second, larger RCT involving 113 active-duty service members recruited from U.S. Army pain management clinics, patients who had stable symptoms with psychotropic medications and a PTSD Checklist-Civilian Version for DSM-IV (PCL-C-4) score greater than 32 received either a right-sided SGB or a sham saline injection at weeks 0 and 2 and were followed for 8 weeks (Olmsted *et al.* 2020). To reduce the secondary gain component, patients undergoing compensation evaluations were excluded from the study. CAPS-5 total symptom severity scores showed a statistically significant adjusted mean change of -12.6 points for SGB and of -6.1 points for sham injection. These results were promising but less generalizable, as the participants had stable disease with their medication regimen, traumatic brain injury was an exclusion criterion, and PTSD symptoms were mild to moderate (Olmsted *et al.* 2020; Raskind 2020).

Advantages of using an SGB include the possibility that it may be perceived by patients as less stigmatizing than medication or psychotherapy because it is a physical procedure (Summers and Nevin 2017) and that, if effective, it is fast acting, working minutes to days after the procedure (Peterson *et al.* 2017). Verification that an SGB was successful can be made within 15 minutes of injection via symptoms including ptosis, miosis, anhidrosis, and enophthalmos, all part of temporary Horner's syndrome (Lipov and Ritchie 2015; Mulvaney *et al.* 2014; Peterson *et al.* 2017). A considerable disadvantage is the need for an anesthesiologist and continuous monitoring in case of accidental intravascular injection (Peterson *et al.* 2017). Other possible adverse effects include severe complications such as bleeding, seizures, pneumothorax, and spinal cord trauma (Lipov and Ritchie 2015). There are methodological issues around a 1992 German questionnaire survey of approximately 39 anesthesiology departments with 45,000 SGBs performed, which reported a rate of severe complications (e.g., convulsions and pneumothorax) of 1.7 per 1,000 (Peterson *et al.* 2017; Wulf and Maier 1992). A 2015 publication on SGB and PTSD showed no adverse outcomes from 250 SGBs conducted under fluoroscopy and suggested that ultrasonographic guidance would further enhance safety (McLean 2015).

The precise mechanism of action of SGB in the treatment of PTSD is unknown. Studies have been limited to 3 months of follow-up (Peterson *et al.* 2017). Longer-term effects have been hypothesized to last as a result of SGB leading to a reduction in nerve growth factor, mediating decreased sympathetic nerve sprouting and norepinephrine availability (Lipov and Ritchie 2015). More studies are needed to assess outcomes and long-term effects in more generalizable populations. SGBs show promise as an adjunct that may reduce some PTSD symptoms that would otherwise serve as barriers to care or successful symptom reduction and remission.

Conclusion and Future Directions

Since the advent of PTSD as an official clinical disorder in DSM-III (American Psychiatric Association 1980), researchers have striven to identify effective pharmacological treatments. Despite the often profound symptom burden and destructive life consequences that result from the disorder, the FDA has approved only two medications for PTSD over the past 40 years. Many categories of standard psychotropic medications, including antipsychotics, mood stabilizers, and antidepressants, are being used, but many patients' symptoms do not respond and too few reach remission. Neuromodulation, particularly with PTSD and comorbid depression, and psychedelic-assisted psychotherapies show promise but do not yet have robust enough evidence for their use over standard care. Evidence-based psychotherapies, such as cognitive-processing therapy and prolonged exposure, are considered first-line treatments for PTSD and have been more effective, with a greater number of completers with remitted PTSD; however, nonresponders remain. Focus on the brain regions involved in treatment response and the mechanism of action in several systems, including the hypothalamic-pituitary-adrenal axis, synaptic plasticity, and neurogenesis, has spawned new targets for research. Examples are summarized below:

- Although the glucocorticoid receptor antagonist mifepristone (RU486) has not been reported to have a significant direct effect in humans as a PTSD treatment to date (DePierro *et al.* 2019), it has been found to improve verbal learning, which may impact the treatment course (Golier *et al.* 2016).
- GSK561679, a corticotropin-releasing factor receptor type 1 (CRF1) antagonist, did not separate from placebo overall but did produce significant symptom reduction in a subset of women who had experienced childhood abuse and were hypothesized to have CRF1 receptor hyperactivity (Dunlop *et al.* 2017).
- Brexanolone, an intravenous formulation of the endogenous neurosteroid allopregnanolone, has been approved for postpartum depression and is being studied for PTSD.
- Studies targeting the neuropeptide Y system (DePierro *et al.* 2019) and factors leading to and promoting resilience spark hope for new treatment approaches to PTSD.

Unlike many psychiatric disorders, PTSD is associated with a stressor event, thereby opening the door for timely research focused not only on treatment but also on prevention of the disorder itself. Agents to assist with extinction recall and memory encoding are being explored, such as the b-adrenergic antagonist propranolol and dopamine precursor L-dopa, which was recently shown to aid in boosting reactivation of amygdala extinction encodings but not in improving extinction recall in women with PTSD (Cisler *et al.* 2020). In addition, a Cochrane Review concluded that there was evidence for hydrocortisone in the role of PTSD prevention (Amos *et al.* 2014). Epigenetic changes and the search for biomarkers to help develop and predict treatment response are beyond the scope of this chapter, but they hold promise for the field in moving to a more personalized medicine approach. What has been clear over the years is that there is not a "one-size-fits-all" treatment for PTSD. Further investigation into different potential subtypes of PTSD may help elucidate differential responses to current and novel treatments.

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CHAPTER 52

Treatment of Obsessive-Compulsive Disorder

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With the publication of DSM-5 (American Psychiatric Association 2013), OCD is no longer considered an anxiety disorder and instead has moved to its own disorder class--Obsessive-Compulsive and Related Disorders. There have been a number of advances in the pharmacological treatment of OCD over the past decade, including new strategies for monotherapy and augmenting with or combining medications. In addition, researchers have begun to explore the use of nutraceuticals, pharmacological enhancement of psychotherapy, and neuromodulation/neurosurgical treatment approaches. In this chapter, we review findings on each of these topics, highlighting key results from randomized controlled trials and select open-label trials of relevance to the treatment of OCD.

OCD is a debilitating psychiatric condition characterized by recurrent intrusive thoughts (obsessions) and repetitive behaviors or mental acts (compulsions) that lead to distress and functional impairment (Stein *et al.* 2019). Once believed to be quite rare, OCD is now recognized to be more common than schizophrenia and a substantial contributor to the global burden of disease (Baxter *et al.* 2014). In the National Comorbidity Survey and subsequent National Comorbidity Survey Replication, the lifetime prevalence rate for OCD was approximately 2.3%, whereas the 12-month prevalence was 1.2% (Kessler *et al.* 2012; Ruscio *et al.* 2010).

A robust evidence base supports both psychotherapeutic and psychopharmacological approaches to treating OCD, the latter of which are the focus of this chapter. Neuromodulation treatments are also reviewed. Pharmacological treatment will relieve symptoms for a majority of patients (Skapinakis *et al.* 2016) and, when combined optimally with cognitive-behavioral therapy (CBT), can help as many as 69% to achieve wellness (i.e., minimal symptoms [Simpson *et al.* 2021]).

This chapter aims to provide practitioners with a focused overview of the state of the art in evidence-based pharmacological treatments for OCD. We review first-and second-line pharmacological treatments for OCD (e.g., serotonin reuptake inhibitors [SRIs], including selective serotonin reuptake inhibitors [SSRIs] and clomipramine), other agents used as monotherapy when these agents are not effective (e.g., serotonin-norepinephrine reuptake inhibitors [SNRIs]), medications used to augment SRIs (e.g., neuroleptics, glutamate modulators, and stimulants), and medications that show promise and are currently being examined (e.g., ketamine). In addition, we discuss recent developments in neuromodulation/neurosurgical approaches to treating OCD, and we highlight differences in the approach to pharmacological treatment of children and adolescents with OCD compared with adults.

The majority of the studies referenced in this chapter use the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to define treatment response. Considered the gold-standard measure of OCD symptoms, the Y-BOCS is a 10-item clinician-rated assessment of obsession and compulsion severity over the past week (Goodman *et al.* 1989b). The scale ranges from 0 to 40, with a score of 16 or greater indicating clinically significant OCD that warrants treatment. The studies in children and adolescents discussed herein use the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS [Scahill *et al.* 1997]), a similar clinician-rated measure adapted for use in pediatric populations. Using the Y-BOCS alone or coupled with other measures such as the Clinical Global Impression Scale (Guy 1976), measures of response and remission have been developed and used in clinical trials. Although the importance of standardizing these outcomes has been discussed (Simpson *et al.* 2006) and global guidelines have been proposed (Mataix-Cols *et al.* 2020), some variations persist, making comparisons across studies more difficult. These variations are noted when necessary in the following review.

Monotherapy for Obsessive-Compulsive Disorder

Table 52-1 summarizes the medications used as monotherapy for OCD.

TABLE 52-1. Monotherapies for obsessive-compulsive disorder

Class	Role in treatment	Clinical considerations	Supporting research
SSRIs	First line (adults), second line after CBT (children and adolescents)	Dosages above the FDA-recommended maximum are occasionally required	Geller *et al.* 2001
		Adverse effects include gastrointestinal upset and sexual dysfunction; risk increases at higher dosages	Goodman *et al.* 1989a
		Minimum trial duration of 8-12 weeks	Hollander *et al.* 2003a Liebowitz *et al.* 2002 March *et al.* 1998 Rasmussen *et al.* 1997 Riddle *et al.* 2001 Tollefson *et al.* 1994
Clomipramine	Second line (adults), third line (children and adolescents), particularly in patients whose symptoms have not	Some evidence suggests slight benefit over SSRIs, although this finding has been inconsistent	DeVeaugh-Geiss *et al.* 1992

Note. 5-HT = 5-hydroxytryptamine (serotonin); CBT = cognitive-behavioral therapy; MAOIs = monoamine oxidase inhibitors; N/A = not available; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

Class	Role in treatment	Clinical considerations	Supporting research
	responded to two or more SSRI trials		
		Greater adverse-effect burden than SSRIs; may cause anticholinergic (e.g., dry mouth, constipation), antihistaminergic (e.g., weight gain, sedation), and anti- a-adrenergic (e.g., hypotension) effects	Karameh and Khani 2015
		Need to monitor plasma levels, maintaining clomipramine-desmethylclomipramine at < 500 ng/mL	Koran *et al.* 2006
		Intravenous use not recommended outside of the most refractory cases	Leonard *et al.* 1991
			March *et al.* 1990
			Stein *et al.* 1992
			Zohar and Judge 1996
SNRIs (venlafaxine, duloxetine)	Can be tried when SSRIs fail but are not FDA approved	Only venlafaxine studied in controlled trials	Dell'osso *et al.* 2008
		Evidence for duloxetine limited to case reports	Denys *et al.* 2004b
		No controlled studies of desvenlafaxine or levomilnacipran	Dougherty *et al.* 2015
			Mowla *et al.* 2016
			Ravizza *et al.* 2001
Mirtazapine	Can be tried in those with symptoms resistant to SSRIs, clomipramine, and SNRIs but is not FDA approved	Antagonist at a_2-adrenergic receptors with a secondary effect of blockade at 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors	Koran *et al.* 2005b
			Pallanti *et al.* 2004

Note. 5-HT = 5-hydroxytryptamine (serotonin); CBT = cognitive-behavioral therapy; MAOIs = monoamine oxidase inhibitors; N/A = not available; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

Class	**Role in treatment**	**Clinical considerations**	**Supporting research**
Other serotonergic agents (MAOIs, vilazodone, vortioxetine)	To be established	Mechanism suggests theoretical potential for efficacy, but untested to date	N/A

Note. 5-HT = 5-hydroxytryptamine (serotonin); CBT = cognitive-behavioral therapy; MAOIs = monoamine oxidase inhibitors; N/A = not available; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

Selective Serotonin Reuptake Inhibitors

The first-line medications for both adults and children with OCD are SSRIs. Of these, fluvoxamine, fluoxetine, and sertraline have been FDA approved for treating OCD in both children and adults. Paroxetine is also FDA approved for treating adult but not pediatric patients with OCD, whereas escitalopram and citalopram are not FDA approved for either group although these medications are often used off-label (Koran *et al.* 2007). As their name implies, SSRIs inhibit the reuptake of serotonin into presynaptic nerve terminals, thereby increasing synaptic serotonin concentrations. This in turn increases inhibition by presynaptic serotonin autoreceptors, which initially decreases but ultimately increases the firing rate of serotonergic neurons as autoreceptors become desensitized with continued exposure (Nutt *et al.* 1999) (for further details, see Chapter 12, "Fluoxetine and Fluvoxamine," and Chapter 13, "Sertraline and Paroxetine").

The efficacy of SSRIs in the treatment of OCD was first established in 1989, when investigators conducted a randomized double-blind, placebo-controlled study in 42 adults with OCD and found that 6-8 weeks of treatment with fluvoxamine ([?] 300 mg/day) led to greater reductions in Y-BOCS scores than placebo (Goodman *et al.* 1989a). Since then, the efficacy of SSRIs in adults with OCD has been confirmed by more than 20 studies in over 3,200 patients (Issari *et al.* 2016; Soomro *et al.* 2008). These include randomized double-blind, placebo-controlled trials of fluoxetine (Tollefson *et al.* 1994), sertraline (Rasmussen *et al.* 1997), and paroxetine (Hollander *et al.* 2003a), in addition to fluvoxamine. Since the initial studies were conducted, meta-analyses continue to support the safety, tolerability, and efficacy of SSRIs for adults with OCD (Issari *et al.* 2016; Skapinakis *et al.* 2016).

Although there have been relatively fewer studies of SSRIs in children and adolescents, large randomized placebo-controlled trials similarly support the safety and superiority of fluvoxamine (Riddle *et al.* 2001), fluoxetine (Geller *et al.* 2001; Liebowitz *et al.* 2002), and sertraline (March *et al.* 1998) to placebo. Subsequent meta-analyses also support moderate to large effect sizes for these agents (Sanchez-Meca *et al.* 2014). However, unlike in adults, meta-analyses of SSRIs in children and adolescents have found that these agents are associated with smaller effect sizes and higher side-effect burden compared with CBT (Sanchez-Meca *et al.* 2014; Watson and Rees 2008). For this reason, most guidelines recommend CBT as a first-line treatment for children and adolescents with mild to moderate OCD (Geller and March 2012), with SSRIs to be used as a second-line approach for patients with severe symptoms or whose symptoms do not respond to an initial trial of CBT.

Few head-to-head comparisons of the six SSRIs listed earlier have been conducted. However, the current data do not support any meaningful differences in efficacy between them, although their adverse effects may vary (Pittenger *et al.* 2021).

Dosage

Compared with dosages used for anxiety or depressive disorders, higher dosages of SSRIs are associated with greater efficacy for treating OCD (Bloch *et al.* 2010; Ninan *et al.* 2006). American Psychiatric Association practice guidelines recommend occasional use of dosages as high as fluvoxamine 450 mg/day, fluoxetine 120 mg/day, sertraline 400 mg/day, paroxetine 100 mg/day, and escitalopram 60 mg/day (Koran *et al.* 2007). However, higher SSRI dosages are also associated with higher rates of treatment dropout as a result of adverse effects such as initial gastrointestinal upset or sexual dysfunction (Stein *et al.* 2019). Thus, optimal dosing requires a careful balance between efficacy and minimization of side effects.

Citalopram has been linked to QTc prolongation on electrocardiogram (ECG) monitoring at higher dosages, leading the FDA to recommend avoiding dosages above 40 mg/day (or 20 mg/day for adults age [?] 60 years) because of the associated risk for cardiac arrhythmia (U.S. Food and Drug Administration 2012). Although subsequent analyses have not revealed a clear association between citalopram and adverse cardiac effects (Hutton *et al.* 2017), treatment with high-dosage citalopram (and perhaps its therapeutically active enantiomer escitalopram) should nonetheless be pursued with caution; ECG monitoring is also advisable for elderly patients and individuals with a history of cardiac events (Kayser 2020).

Treatment Duration

Patients with OCD may also require a longer duration of SSRI treatment than those with anxiety or depressive disorders. American Psychiatric Association guidelines recommend a treatment duration of 8-12 weeks to determine efficacy (Koran *et al.* 2007). Two meta-analyses reported that initial improvement may occur as early as 2 weeks after starting an SSRI, and the greatest incremental improvements tended to accrue earlier in treatment (Issari *et al.* 2016; Varigonda *et al.* 2016). Moreover, in an open-label trial of fluoxetine in treatment-naive patients, those whose symptoms improved the most during the first 4 weeks were most likely to develop a full clinical response (i.e., [?] 35% decrease in Y-BOCS scores) by week 12 (da Conceicao Costa *et al.* 2013). These data suggest that early response may help predict the long-term benefit of a particular SSRI for patients with OCD, although some with limited early improvement will still achieve a response to a trial of 12 weeks or longer (Rasmussen *et al.* 1997).

For patients who achieve a clinically meaningful response, treatment for an additional 12-24 months is generally recommended (Baldwin *et al.* 2014; Greist *et al.* 2003). To our knowledge, there are no published data regarding the clinical outcome of lowering the SSRI dosage during this maintenance phase of treatment. However, a meta-analysis reported that symptoms recurred for approximately 36% of patients who discontinued SSRIs (Batelaan *et al.* 2017). Extended treatment may therefore be necessary to prevent relapse in some cases.

Side Effects

Common side effects of SSRIs include gastrointestinal upset (e.g., nausea, diarrhea), headache, dry mouth, drowsiness, insomnia, nervousness or restlessness, and sexual dysfunction (Chang *et al.* 2022). These effects occur most frequently during the first 2 weeks after initiation, although approximately half of patients report experiencing at least one side effect during maintenance treatment (Hu *et al.* 2004). Less commonly, weight gain may occur during SSRI treatment. Rare and severe side effects of SSRIs include increased risk for bleeding, syndrome of inappropriate antidiuretic hormone secretion, and serotonin syndrome (Chang *et al.* 2022).

Studies suggesting that SSRIs may increase the risk for suicidal thoughts and behaviors in children, adolescents, and young adults led the FDA to issue a black box warning regarding their use in these populations (U.S. Food and Drug Administration 2004). Thus, careful assessment of the risks and benefits of SSRIs is critical before starting treatment in young people, as is close monitoring for clinical worsening and the emergence of suicidality once treatment has begun.

Discontinuation and Relapse Management

The decision to discontinue medications should be made with the patient's informed consent following discussion of the known risks (e.g., relapse, withdrawal symptoms) and benefits (e.g., resolution of SSRI-induced sexual dysfunction). Switching to a longer-acting SSRI (e.g., fluoxetine) and tapering medications gradually over the course of weeks to months (vs. days to weeks) may reduce the risk for withdrawal and/or relapse (Horowitz and Taylor 2019). Although few studies have evaluated the efficacy of different relapse prevention strategies, experts generally recommend developing a relapse management plan in collaboration with the patient and their family, which may include starting CBT or reinitiating medication (Fineberg *et al.* 2020).

Treatment Resistance

Unfortunately, only a minority of patients with OCD will achieve minimal symptoms (defined as a Y-BOCS score [?] 12) after an initial SRI trial (Farris *et al.* 2013). When this happens, evidence-based pharmacological strategies include optimizing the dosage and duration of treatment, switching to another medication, or augmenting with an additional medication (Pittenger *et al.* 2021). Of note, there is also strong evidence to support combining medication with CBT for OCD at this stage, with one trial showing larger effect sizes for augmenting SSRIs with CBT versus augmenting with risperidone (Simpson *et al.* 2013). Although a detailed discussion of CBT for OCD is beyond the scope of this chapter, CBT is a first-line treatment for OCD alongside SSRIs and should always be considered in cases of SSRI treatment resistance.

When SSRI treatment is ineffective despite a trial of adequate dosage and duration, switching to a different agent is a reasonable next step. Although switching to another SSRI may help some patients, the likelihood of success decreases with each additional trial (Pittenger 2021). Switching to clomipramine is more likely to be beneficial when the response to a first or second SSRI is limited (Koran *et al.* 2007).

Clomipramine

Clomipramine is a tricyclic antidepressant and potent, nonselective SRI (Murphy *et al.* 1989). By inhibiting norepinephrine, acetylcholine, and histamine reuptake, clomipramine and other tricyclic antidepressants also increase activity at the receptors for these neurotransmitters. Clomipramine was first identified as a potential OCD treatment in the 1960s (Fernandez Cordoba and Lopez-Ibor Alino 1967). Subsequently, a pair of landmark studies in a total of 520 patients (study 1, n = 239 adults with OCD symptoms for at least 2 years; and study 2, n = 281 adults with OCD symptoms for at least 1 year) found that 10 weeks of clomipramine treatment was generally well tolerated, was significantly more effective than placebo, and led to 38% and 41% reductions in Y-BOCS scores, respectively (Clomipramine Collaborative Study Group 1991). These studies established clomipramine's efficacy and ultimately led to its becoming the first FDA-approved treatment for OCD in the United States. Meta-analyses suggest that clomipramine is slightly more efficacious than SSRIs (Hirschtritt *et al.* 2017). However, the initial clomipramine trials included fewer patients with treatment-resistant OCD compared with more recent SSRI studies (Stein *et al.* 2019), and a series of direct comparisons between SSRIs and clomipramine found their efficacies to be equivalent (Bisserbe *et al.* 1997; Lopez-Ibor *et al.* 1996; Zohar and Judge 1996).

Compared with SSRIs, clomipramine's side-effect profile is less favorable. Clomipramine's activity at nonserotonergic receptor targets gives it the potential to cause anticholinergic effects (e.g., dry mouth, constipation), antihistaminergic effects (e.g., sedation, weight gain), and anti-a-adrenergic effects (e.g., hypotension). Clomipramine has also been linked to a reduced seizure threshold and to greater risk for cardiac arrhythmias; as a result of the latter, ECG results should be monitored periodically during clomipramine treatment (Koran *et al.* 2007). To prevent clomipramine toxicity, treatment guidelines recommend avoiding clomipramine dosages above the FDA maximum of 250 mg/day in most cases (Koran *et al.* 2007). Although not correlated with treatment efficacy (Pittenger 2021), plasma levels of clomipramine and its metabolite desmethylclomipramine can help with toxicity monitoring and should be

kept at a combined level of less than 500 ng/mL (Koran *et al.* 2007). Given that SSRIs are similarly effective, are more tolerable, and require less intensive safety monitoring, clomipramine should generally be reserved for use after SSRIs.

Clomipramine treatment has also been evaluated in children and adolescents with OCD, including two trials that supported its FDA approval for patients older than age 10 years. The first was a 10-week randomized double-blind, placebo-controlled trial of clomipramine versus placebo in 16 children and adolescents with OCD (March *et al.* 1990). The investigators found a trend toward substantial benefit from clomipramine over placebo that did not reach statistical significance; however, post hoc analyses revealed significant improvement in CY-BOCS scores among patients with neurological symptoms (March *et al.* 1990). In the second trial, an 8-week randomized double-blind, placebo-controlled trial in 60 children and adolescents with OCD at five individual sites, DeVeaugh-Geiss *et al.* (1992) found a mean reduction in CY-BOCS scores of 37% in the clomipramine group compared with 8% in the placebo group. Although meta-analyses indicate that effect sizes for clomipramine are comparable to or larger than those for SSRIs in the treatment of children and adolescents with OCD (Varigonda *et al.* 2016; Watson and Rees 2008), this agent has various adverse effects, and its use with pediatric populations is generally reserved for cases in which multiple trials of CBT and SSRIs have failed (Geller and March 2012).

Although the abovementioned studies all used oral clomipramine, intravenous clomipramine has also been tested in a few small trials in adults with OCD. By preventing first-pass metabolism, this formulation theoretically could mitigate side effects (Fallon *et al.* 1992) while also quickly generating therapeutic dosages to hasten symptom relief (Koran *et al.* 1997). Whereas some small trials reported intravenous clomipramine to be more effective in patients whose symptoms responded poorly to oral formulations (Fallon *et al.* 1992, 1998; Karameh and Khani 2015; Koran *et al.* 1997), results from other studies were mixed (Koran *et al.* 2006; Mundo *et al.* 1999). Because its efficacy remains equivocal and its availability is limited, intravenous clomipramine is rarely used.

Other Serotonergic Agents

Only SSRIs and clomipramine have been definitively shown to be beneficial as standalone pharmacotherapies for OCD. However, other agents have demonstrated some promise and may be considered when patients' symptoms do not respond to SSRIs and/or clomipramine. Although these agents act by a variety of mechanisms, each interacts with the serotonin system to an extent. In all trials reviewed next, treatment response was defined as a Y-BOCS score reduction of at least 35% unless otherwise specified.

Serotonin-Norepinephrine Reuptake Inhibitors

Given the established efficacy of SRIs, other serotonergic agents such as SNRIs could also theoretically improve OCD symptoms. However, there have only been a few small SNRI trials in patients with OCD to date, with mixed results.

Venlafaxine. Of the SNRIs, venlafaxine is the most studied in patients with OCD. In a 12-week randomized double-blind comparison trial in 150 adults with OCD, investigators found equivalent rates of clinical response and adverse effects for venlafaxine ([?] 300 mg/day) and paroxetine ([?] 60 mg/day) (Denys *et al.* 2003). A second trial in 47 patients used a similar enrollment strategy and design to compare the effects of venlafaxine ([?] 350 mg/day) and clomipramine ([?] 225 mg/day) (Albert *et al.* 2002). Similar efficacy was shown for both agents, but individuals treated with venlafaxine experienced fewer adverse effects (Albert *et al.* 2002). In addition, two studies evaluated the effects of switching to either another SSRI or venlafaxine for adults with OCD that responded poorly to an initial SSRI trial. One trial reported greater response among participants switched to venlafaxine (Ravizza *et al.* 2001), whereas the other found higher response rates (defined in this study as a Y-BOCS score reduction of at least 25%) for those who received an alternative SSRI (Denys *et al.* 2004b). An observational study from an Indian specialty clinic reported that approximately 45% of adults with symptomatic OCD despite SSRI treatment achieved response when switched to venlafaxine (Balachander *et al.* 2019).

Duloxetine. Several case reports and at least one case series describe adult patients with OCD whose symptoms improved after switching from an SSRI to duloxetine (Dell'osso *et al.* 2008). A small open-label trial in 20 medication-free adults with OCD reported that around half responded to 17 weeks of treatment with duloxetine ([?] 120 mg/day), but 35% did not complete the protocol (Dougherty *et al.* 2015). Finally, Mowla *et al.* (2016) conducted a controlled trial of 46 patients with OCD symptoms that did not respond to initial SSRI treatment. Patients were switched to 12 weeks of treatment with duloxetine versus a second SSRI, and response rates (defined as a Y-BOCS score reduction [?] 25%) and mean reductions in Y-BOCS scores were similar for both groups (total Y-BOCS score decrease of 10.5 vs. 10.6, respectively [Mowla *et al.* 2016]).

Other serotonin-norepinephrine reuptake inhibitors. Controlled studies of the other two FDA-approved SNRIs, desvenlafaxine and levomilnacipran, have not been conducted in patients with OCD.

Mirtazapine

Mirtazapine is an atypical antidepressant that acts primarily as an antagonist at a_2-adrenergic receptors. It also has secondary effects on serotonergic signaling, including blockade of the serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors. One open-label trial found moderate symptomatic improvement among 30 adults with OCD who received mirtazapine monotherapy, titrated to 60 mg/day, over 12 weeks (Koran *et al.* 2005b). In another study, 49 adults with OCD were randomly assigned to 12 weeks of treatment with citalopram (20-80 mg/day) either alone or combined with mirtazapine (15-30 mg/day). Mirtazapine seemed to accelerate the initial response to citalopram, although it did not improve overall efficacy (Pallanti *et al.* 2004). With so few data, the benefit of mirtazapine to patients with OCD remains equivocal.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) act by inhibiting monoamine oxidase activity, thus preventing the breakdown of monoamine neurotransmitters (e.g., serotonin, norepinephrine, and dopamine) and increasing their availability (Hendriksen and Groenink 2015). Despite these agents' efficacy in the treatment of depression and anxiety disorders, trials of MAOIs in OCD are currently scarce; the existing trials had small sample sizes and yielded mixed results. One double-blind, randomized crossover trial in 13 adults with OCD found significant symptomatic improvement following treatment with clomipramine but not the MAOI clorgyline (which is not currently available in the United States [Insel *et al.* 1983b]). A second double-blind trial comparing 12 weeks of treatment with either clomipramine or phenelzine in 30 adults with OCD reported that both agents significantly improved symptoms but did not differ from each other (Vallejo *et al.* 1992). Finally, a third double-blind study compared phenelzine to fluoxetine and placebo in 54 adults with OCD and found that both agents, although significantly better than placebo, led to only mild improvement (< 3 points on the Y-BOCS [Jenike *et al.* 1997]).

A recent case series described nine adults whose OCD had failed to respond to phenelzine treatment in at least two prior medication trials (Grant *et al.* 2021a). Three patients experienced marked response, three experienced moderate, and three experienced no response to phenelzine treatment. Patients whose symptoms improved the least did not have a comorbid anxiety disorder (Grant *et al.* 2021a). Although these results suggest that MAOIs may have some value for treating patients with OCD with comorbid anxiety disorders, the current data are insufficient to support their use outside of patients whose symptoms are unresponsive to multiple medication trials.

Novel Serotonergic Drugs

Over the past decade, two novel serotonergic drugs (vilazodone and vortioxetine) were FDA approved for the treatment of depression. In addition to inhibiting serotonin reuptake, these agents have unique mechanistic profiles compared with other approved drugs: vilazodone is a 5-HT$_{1A}$ receptor partial agonist and a moderate inhibitor of both norepinephrine and dopamine reuptake, whereas vortioxetine is a 5-HT$_{1A}$ full agonist, 5-HT$_{3}$ antagonist, and modulator of several other serotonin receptor subtypes (Faquih *et al.* 2019). Although their novel activities suggest that these agents could be useful for treating OCD, only two case reports describe positive effects from vortioxetine treatment in patients with the disorder (De Berardis *et al.* 2017; Naguy *et al.* 2019), and there are no published data regarding vilazodone.

Serotonin Reuptake Inhibitor Augmentation and Combination Strategies

In the event of a partial response to SRI monotherapy, the next step is typically to combine an SRI with another agent. Of the combinatorial strategies, adding an antipsychotic has the greatest evidence base from randomized controlled trials. There is also some evidence to support adding a glutamate modulator, combining an SSRI with clomipramine, or adding a stimulant.

Table 52-2 summarizes the medications used in augmentation/combination treatment approaches for OCD.

TABLE 52-2. Pharmacological combination and augmentation of serotonin reuptake inhibitors

Medication class/ role in treatment	Clinical considerations	Supporting research
Antipsychotics		
Augmentation of SRIs in adults	Meta-analyses show the greatest support for risperidone ([?] 2-3 mg/day); studies also support aripiprazole ([?] 10-15 mg/day).	Ercan *et al.* 2015
	Haloperidol may have some additional benefit for patients with comorbid tics but may be difficult to tolerate because of extrapyramidal symptoms (e.g., tremor, muscle rigidity) and other side effects.	Grillault Laroche and Gaillard 2016
	There is limited evidence to support using paliperidone, olanzapine, or quetiapine.	Hollander *et al.* 2003b
	Unlike with SRIs, there is no evidence of additional benefit from high-dosage antipsychotics.	McDougle *et al.* 1994, 2000
	Clozapine may induce OCD symptoms, possibly due to 5-HT$_{2A/2C}$ receptor antagonism.	Muscatello *et al.* 2011
	Not recommended for children and adolescents, given limited data and risk for weight gain or metabolic syndrome and other side effects.	Pessina *et al.* 2009
		Ravizza *et al.* 1996
		Sayyah *et al.* 2012b
	Simpson *et al.* 2013	
Glutamate modulators		

Note. 5-HT = 5-hydroxytryptamine (serotonin); NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Medication class/ role in treatment	Clinical considerations	Supporting research
Augmentation of SRIs in adults	NAC is recommended as an initial agent given its favorable safety profile, availability over the counter in the United States, and reasonable evidence of benefit. Meta-analyses found that NAC ([?] 3,000 mg/day) had moderate benefits when added to SRI treatment in adults and children with OCD.	Afshar *et al.* 2012
	Askari *et al.* 2022	
	Riluzole, troriluzole, topiramate, lamotrigine, gabapentin, pregabalin, glycine, sarcosine, and amantadine have all been studied in small trials but cannot be recommended based on current data.	Gadallah *et al.* 2020
	Memantine ([?] 20 mg/day) had modest benefits in controlled trials in adults. As a result of its greater risk for adverse effects (e.g., fatigue) and concerns regarding the homogeneity of the supporting studies, it is recommended as a second-line agent in patients whose symptoms are unresponsive to NAC.	Ghaleiha *et al.* 2013 Hezel *et al.* 2009 Kishi *et al.* 2018 Lafleur *et al.* 2006 Paydary *et al.* 2016 Rodriguez *et al.* 2016a
Sarris *et al.* 2015		
Combination SSRIs and clomipramine		
Only SSRI-resistant cases in adults	Typically involves adding low-dosage clomipramine (< 75 mg/day) to an SSRI, with the goal of enhancing serotonergic tone while minimizing the risk for clomipramine adverse effects.	Diniz *et al.* 2010, 2011
	Small controlled trials of this approach had mixed results.	Marazziti *et al.* 2008
	May increase risk for adverse effects (e.g., QTc prolongation, sexual side effects) due to pharmacodynamic and pharmacokinetic interactions.	
Not recommended outside of refractory cases in adult patients.		
Other augmentation agents		

Note. 5-HT = 5-hydroxytryptamine (serotonin); NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Medication class/ role in treatment	**Clinical considerations**	**Supporting research**
Only SSRI-resistant cases in adults	Other agents showing efficacy in small controlled trials include stimulants (amphetamine), pindolol, and the 5-HT_{3A} receptor antagonists ondansetron, granisetron, and tropisetron.	Askari *et al.* 2012 Kalyani *et al.* 2017 Koran *et al.* 2009 Sassano-Higgins and Pato 2015 Shalbafan *et al.* 2019
Sharafkhah *et al.* 2019		

Note. 5-HT = 5-hydroxytryptamine (serotonin); NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Antipsychotics

Multiple placebo-controlled studies suggest that antipsychotics (i.e., dopamine D_2 receptor antagonists) have modest benefits for adults with OCD that responds incompletely to SRIs, although only around one-third of patients will benefit (Bloch *et al.* 2006; Dold *et al.* 2015; Veale *et al.* 2014; Zhou *et al.* 2019). Improvement with antipsychotic augmentation tends to occur in the initial 2-4 weeks of treatment; thus, prolonged trials are generally not recommended (Fineberg *et al.* 2015). Although there have been no dosage-finding studies of antipsychotics in patients with OCD, low dosages are generally recommended because of these agents' association with weight gain, metabolic syndrome, and other adverse effects; furthermore, there is little evidence that higher dosages lead to additional improvement (Pittenger 2021). At any dosage, the risk/benefit ratio of antipsychotic augmentation should be continuously reevaluated throughout treatment (Matsunaga *et al.* 2009). Of note, there have been no controlled trials of antipsychotics in children and adolescents with OCD. Given their potential for long-term adverse effects in children and adolescents (e.g., weight gain, metabolic syndrome), antipsychotics should generally be avoided in this population.

Haloperidol

Haloperidol was one of the first augmentation agents to be studied in OCD and is the most widely researched of the first-generation antipsychotics (Pittenger 2021). Adults with OCD whose symptoms were unresponsive to SSRIs experienced symptomatic improvement with haloperidol augmentation in one open-label and two double-blind, placebo-controlled trials (Li *et al.* 2005; McDougle *et al.* 1990, 1994). These studies found higher response rates (defined as a Y-BOCS score reduction [?] 35%) among patients with a history of tics. However, support for a specific benefit to patients with OCD and comorbid tics was inconsistent in subsequent meta-analyses (Bloch *et al.* 2006; Veale *et al.* 2014; Zhou *et al.* 2019). Haloperidol was also poorly tolerated in these studies, owing to high rates of extrapyramidal symptoms (e.g., tremor, rigidity, or dyskinesias). Although clarification of these findings is needed, given the available data, it is reasonable to reserve haloperidol augmentation for patients with OCD with contraindications to second-generation antipsychotics (which are less likely to cause extrapyramidal symptoms) or those with comorbid tics.

Risperidone

Risperidone is the augmentation agent that has been most tested in controlled trials. Three small randomized placebo-controlled trials in adults with OCD that did not respond to prior SSRI treatment found that symptoms improved with risperidone augmentation (Erzegovesi *et al.* 2005; Hollander *et al.* 2003b; McDougle *et al.* 2000). The average risperidone dosage in these studies was between 2 and 3 mg/day. Subsequent meta-analyses suggested that risperidone augmentation may have greater efficacy compared with other antipsychotics (Dold *et al.* 2015; Veale *et al.* 2014; Zhou *et al.* 2019). However, a trial in adults with SRI-treated OCD who still had clinically significant symptoms reported no difference between those randomly assigned to 8 weeks of risperidone (n = 40) and those receiving placebo augmentation; patients randomly assigned to CBT augmentation (n = 40) had better outcomes than both the risperidone and placebo augmentation groups (Simpson *et al.* 2013). Instead of suggesting that risperidone augmentation is ineffective, these findings may reflect sampling differences between this study and the three prior risperidone trials. For example, all but two participants in the study by Simpson *et al.* (2013) achieved at least a partial response

to their SSRI, whereas participants in the previous trials had symptoms that were completely unresponsive to SSRIs. Moreover, participants recruited to a trial in which they could receive medication or CBT (as in Simpson *et al.* 2013) may have different treatment preferences than those who enroll in a medication trial (as in the previous studies), and these preferences can affect the outcome of treatment (Patel and Simpson 2010; Patel *et al.* 2017). Together, the results of these four studies support pursuing CBT as a first alternative when patients' symptoms do not respond to SRI treatment; for patients who do not obtain symptom improvement with or are uninterested in CBT, a trial of risperidone is a reasonable alternative.

Aripiprazole

Several studies have also examined aripiprazole augmentation in patients with OCD symptoms that were partially or completely unresponsive to ongoing SRI treatment. For example, two open-label trials in 9 and 20 adults with SSRI-unresponsive OCD (Dar *et al.* 2021; Pessina *et al.* 2009) found small but statistically significant improvements in Y-BOCS scores following augmentation. In addition, two placebo-controlled OCD trials--one in 30 adults whose symptoms were unresponsive to SSRIs or clomipramine (Muscatello *et al.* 2011) and another in 39 adults with SSRI-unresponsive symptoms (Sayyah *et al.* 2012b)--found greater improvement in Y-BOCS scores with aripiprazole augmentation compared with placebo. In a recent head-to-head comparison, aripiprazole also showed greater efficacy than quetiapine augmentation of SSRI treatment in 33 adults with OCD over 12 weeks of treatment (Talaei *et al.* 2020). In these studies, aripiprazole was generally well tolerated at dosages between 10 and 15 mg/day.

Although there have been no controlled trials of any antipsychotics in children and adolescents with OCD to date, a few case series and small open-label trials have examined the effects of aripiprazole in this population. Aripiprazole is potentially of greater interest in treating children and adolescents, given its lower likelihood of causing weight gain, metabolic syndrome, and other adverse effects compared with risperidone and other antipsychotics. Indeed, a review of this sparse literature suggests that aripiprazole is tolerable in children and adolescents with OCD and may have modest benefits when added to an SSRI (Thamby and Jaisoorya 2019). Nonetheless, these results must be confirmed in controlled trials before aripiprazole can be recommended for treating children and adolescents with OCD in clinical practice.

Quetiapine

Several studies have evaluated quetiapine's efficacy in augmenting SRI treatment of adults with OCD, with mixed results. For example, two placebo-controlled randomized trials in 27 and 40 adults with SRI-unresponsive OCD found decreased Y-BOCS scores after 8 weeks of quetiapine augmentation of SRI treatment (Atmaca *et al.* 2002; Denys *et al.* 2004a). However, three randomized placebo-controlled trials in 49, 21, and 40 adults with SRI-unresponsive OCD found that quetiapine did not improve Y-BOCS scores compared with placebo (Carey *et al.* 2005; Fineberg *et al.* 2006; Kordon *et al.* 2008). Head-to-head comparisons involving quetiapine augmentation have also been equivocal. In one trial in 44 female adult inpatients with OCD that responded poorly to SRI treatment, investigators found a greater response rate for quetiapine augmentation compared with aripiprazole; however, the mean reduction in Y-BOCS scores for both groups was small (< 3 points) and baseline symptoms were more severe in the aripiprazole group (Shoja Shafti and Kaviani 2015). In another trial, 40 adults with OCD and poor fluoxetine response received quetiapine, clomipramine, or placebo; both clomipramine and placebo led to greater improvement in Y-BOCS scores than quetiapine (Diniz *et al.* 2011). Based on these data, there is currently insufficient evidence to support quetiapine augmentation of OCD treatment in most situations.

Olanzapine

There have been several open-label studies of olanzapine augmentation of OCD treatment but only three controlled trials to date. A double-blind, placebo-controlled trial in 26 adults with an incomplete SSRI response reported that 46% achieved response to olanzapine (i.e., [?] 25% reduction in Y-BOCS scores), whereas none achieved response with placebo (Bystritsky *et al.* 2004). However, a similarly designed trial in 48 adults meeting similar criteria failed to replicate this finding (Shapira *et al.* 2004). More recently, a trial comparing olanzapine, aripiprazole, and L-methylfolate in 56 adults with OCD and an incomplete SSRI response found modestly greater reductions in symptoms with both olanzapine and aripiprazole treatment compared with L-methylfolate (which itself had little effect [Dar *et al.* 2021]). Weight gain is common with olanzapine and was reported by patients in all three of the abovementioned studies. Further evaluation of the efficacy of olanzapine augmentation in OCD is needed before its use can be recommended.

Paliperidone

One randomized controlled trial examined the effects of paliperidone versus placebo in 34 adults with OCD who experienced an incomplete response to SSRIs (Storch *et al.* 2013). Although OCD symptoms improved for patients who received paliperidone over 8 weeks, this effect did not differentiate from placebo. Until better-powered studies can be conducted, the efficacy of paliperidone augmentation in OCD is considered inconclusive.

Clozapine and Antipsychotic-Induced Obsessive-Compulsive Disorder Symptoms

Despite its efficacy for psychosis, clozapine is not thought to be effective in OCD; however, this has never been formally tested in a clinical trial (Pittenger *et al.* 2021). In fact, there is evidence that clozapine can induce OCD symptoms in some patients, which may relate to its antagonism of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors (Grillault Laroche and Gaillard 2016). There are case reports of other antipsychotics inducing OCD symptoms when delivered without an SSRI, although these associations have not been clearly established (Pittenger *et al.* 2021). Although a detailed discussion is beyond the scope of this chapter, strategies to manage clozapine-induced OCD symptoms in individuals with psychotic disorders may include dosage reduction and addition of aripiprazole (Kim *et al.* 2020).

Stimulants/Amphetamine

Although dopamine receptor antagonists (i.e., antipsychotics) are more commonly used, stimulant medications that increase dopaminergic signaling have also been studied as potential OCD treatments. Two small placebo-controlled crossover trials in

12 and 11 patients with OCD found that a single dose of D-amphetamine (30 mg) led to greater acute improvement in symptoms than placebo (Insel *et al.* 1983a; Joffe *et al.* 1991). The second of these trials also evaluated a single dose of methylphenidate (40 mg) but failed to find any difference in effect compared with placebo (Joffe *et al.* 1991), a finding shared by an earlier open-label trial of a single dose of methylphenidate in 11 patients with OCD (Joffe and Swinson 1987).

Subsequent trials focused on use of stimulants to augment SRI treatment. A small double-blind trial in 21 patients with refractory OCD found that both D-amphetamine (30 mg) and caffeine (which was used as an active comparator) improved symptoms when added to an SRI (Koran *et al.* 2009). However, interpreting these data is challenging, considering that one-third of the patients were taking SNRIs, which do not have established efficacy in OCD. More recently, a randomized double-blind trial in 44 adults with OCD unresponsive to SRIs found significantly greater improvement in symptoms over 8 weeks when methylphenidate (36 mg/day) was added to fluvoxamine (250 mg/day) compared with placebo (Zheng *et al.* 2019).

These preliminary data suggest that stimulant augmentation may be helpful in patients with an inadequate SRI response. However, stimulants may also induce OCD symptoms in some individuals (Jhanda *et al.* 2016). To confirm the efficacy of stimulants in patients with OCD and better understand their risk/benefit profile, rigorous testing in larger controlled studies is needed.

Combination Selective Serotonin Reuptake Inhibitor and Clomipramine

Another strategy that has been used in patients who did not obtain an adequate response to SSRI monotherapy is to combine an SSRI with clomipramine. This approach typically involves adding a low dosage of clomipramine (< 75 mg/day) to a maximum-dosage SSRI, with the goal of increasing the overall serotonergic effect while minimizing adverse effects that may occur with higher clomipramine dosages (Andrade 2013). This approach was reported to be effective in case series of both children and adolescents (Figueroa *et al.* 1998; Simeon *et al.* 1990) and adults (Browne *et al.* 1993) with SRI-refractory OCD. An open-label study in 24 adults with OCD that did not respond to initial treatment with clomipramine 150 mg/day found that adding sertraline 50 mg/day was more effective and better tolerated than increasing clomipramine to 250 mg/day (Ravizza *et al.* 1996). Similarly, another open-label study in 16 patients with OCD unresponsive to citalopram treatment found adding clomipramine to be more effective than continuing citalopram alone (Pallanti *et al.* 1999). In a third open-label trial, 20 patients with OCD with poor response to an SSRI and also to current treatment with clomipramine (mean dosage = 164 mg/day) were started on adjunct citalopram (mean dosage = 38 mg/day). Over the course of 48 weeks of treatment, Y-BOCS scores decreased by 30% on average and around half of patients were considered responders (Marazziti *et al.* 2008).

These open-label studies prompted a controlled trial in which 54 adult patients with OCD unresponsive to fluoxetine monotherapy were randomly assigned to clomipramine augmentation (maximum dosage = 75 mg/day), quetiapine augmentation (maximum dosage = 200 mg/day), or placebo. Fluoxetine was continued at 40 mg/day for participants in the active augmentation groups but increased to 80 mg in the placebo group. The participants who received quetiapine showed little improvement, whereas both the placebo group (with high-dosage fluoxetine) and the clomipramine group experienced a 25% decrease in Y-BOCS scores (Diniz *et al.* 2011). In contrast, another controlled trial by the same investigators did not find the combination of clomipramine and an SSRI to be effective; 21 adults whose symptoms did not respond to 12 weeks of SSRI treatment were continued on their SSRI and randomly assigned to augmentation with either clomipramine 75 mg/day or quetiapine. After 4 weeks of treatment, neither group showed significant improvement in OCD symptoms (Diniz *et al.* 2010).

When an SSRI and clomipramine are used in combination, their additive serotonergic effects may increase the risk of side effects, such as sexual dysfunction, QTc prolongation, seizures, and serotonin syndrome (Andrade 2013). Pharmacokinetic interactions may further increase this risk; for example, the cytochrome P450 (CYP) enzymes CYP1A2, CYP3A4, and CYP2C19 contribute to clomipramine's metabolism, whereas CYP2D6 is involved in metabolizing both clomipramine and its active metabolite desmethylclomipramine. SSRIs that inhibit these enzymes may therefore increase serum clomipramine levels and thus heighten the risk for adverse events. Fluoxetine, fluvoxamine, paroxetine, and to a lesser extent sertraline may all substantially elevate clomipramine levels, whereas studies of citalopram and escitalopram suggest that they have little effect on clomipramine levels (Taylor 1995). Conversely, clomipramine's inhibition of CYP2D6 may increase serum levels of SSRIs that are metabolized by this enzyme (fluoxetine, sertraline, paroxetine, citalopram, and escitalopram, but not fluvoxamine [Szegedi *et al.* 1996]). However, these effects may be less clinically significant when one considers that SSRIs are better tolerated than clomipramine and that most agents in this class are metabolized by several CYP enzymes in addition to CYP2D6 (Andrade 2013).

Overall, the evidence that favors combining an SSRI with clomipramine is too limited and the associated risks are too high to support the use of this strategy in most clinical scenarios. This approach may be helpful in some treatment-refractory cases, with the proviso that periodic monitoring of plasma levels and ECG results is important to avoid toxicity.

Other Augmentation Agents

Pindolol

Pindolol is an antihypertensive drug and antagonist of both b-adrenergic and 5-HT$_{1A}$ receptors, the latter of which are autoreceptors that decrease serotonin release when stimulated. By inhibiting 5-HT$_{1A}$ activity, pindolol may increase serotonin release and thus play a role in augmenting SRIs for OCD. To date, only two placebo-controlled studies of pindolol augmentation have been conducted in OCD: one in 15 adults with paroxetine-unresponsive symptoms (Dannon *et al.* 2000) and one in 16 adults with fluoxetine nonresponse (Mundo *et al.* 1998). The former (Dannon *et al.* 2000) reported that OCD symptoms were moderately more reduced following pindolol augmentation versus placebo, whereas the latter (Mundo *et al.* 1998) found no difference between pindolol and placebo. A subsequent meta-analysis including these studies and two earlier studies without placebo controls also failed to identify differences between pindolol and placebo, although only four studies were included (Sassano-Higgins and Pato 2015). Further research is needed before pindolol augmentation can be recommended in OCD treatment.

Buspirone

Buspirone, a 5-HT$_{1A}$ receptor partial agonist, is FDA approved for generalized anxiety disorder and showed early promise in a small controlled study in patients with OCD (Pato *et al.* 1991). However, a series of controlled trials subsequently found buspirone to have minimal effect on OCD symptoms (Jenike and Baer 1988; Markovitz *et al.* 1990; McDougle *et al.* 1993; Pigott *et al.* 1992). Thus, buspirone augmentation is not currently recommended in OCD treatment, although it may help some patients with comorbid anxiety disorders.

Serotonin Type 3A Receptor Antagonists

Three 5-HT$_{3A}$ receptor antagonists (ondansetron, granisetron, and tropisetron) have been tested as augmentation agents. These medications are widely used as antiemetics and, although not often prescribed in psychiatry, have garnered interest as potential OCD treatments because of their excellent safety profiles and ability to reduce OCD-like behaviors in some animal models (Serata *et al.* 2015). Ondansetron was initially tested as monotherapy in adults with OCD in two small controlled studies, with equivocal results (Broocks *et al.* 1998; Hewlett *et al.* 2003). Subsequent studies focused on augmentation approaches. In two small controlled OCD trials (n = 14 and 20), ondansetron 0.5-1 mg/day was added to ongoing SSRI treatment in adults whose symptoms had responded poorly to the initial treatment (Pallanti *et al.* 2009, 2014). Patient symptoms improved over the course of both 12-week trials; the second study also reported that two-thirds of responders experienced relapse in the 4 weeks after completing the protocol and stopping ondansetron (Pallanti *et al.* 2014). However, these studies used single-blinded designs (i.e., raters were aware of the study conditions) and lacked placebo controls.

The remainder of the 5-HT$_{3A}$ receptor antagonist trials have been conducted in Iranian patients. One study in adults with OCD randomly assigned participants to 8 weeks of treatment with either fluoxetine 20 mg/day and ondansetron 4 mg/day or fluoxetine and placebo (Soltani *et al.* 2010). A second trial with a similar design randomly assigned participants to either fluvoxamine 200 mg/day and ondansetron 8 mg/day or fluvoxamine and placebo (Heidari *et al.* 2014). Participants in both trials had larger symptomatic improvements with ondansetron augmentation than with placebo. Similar results were obtained in two trials in which adults with OCD were randomly assigned to treatment with fluvoxamine 200 mg/day and either a 5-HT$_{3A}$ receptor antagonist or placebo. One study used granisetron 2 mg/day (Askari *et al.* 2012), and the other used tropisetron 10 mg/day (Shalbafan *et al.* 2019). Finally, in a controlled trial in 135 patients whose symptoms had responded poorly to SSRIs, participants were randomly assigned to 14 weeks of augmentation with ondansetron, granisetron, or placebo (Sharafkhah *et al.* 2019). At week 14, participants in both active treatment groups had fewer symptoms than those in the placebo group, although the remission rate was higher in the ondansetron group. Although interesting, these findings should be interpreted with caution, considering that all five trials were conducted in the same geographic region. Indeed, a recent case series of 30 patients who received ondansetron augmentation in an Indian specialty clinic found that only 2 patients

showed response to this treatment, and nearly 80% discontinued the medication because of lack of efficacy (Kalyani *et al.* 2017). In the United States, a multisite randomized controlled trial of ondansetron augmentation was terminated because of a lack of efficacy (ClinicalTrials.gov 2013). Before 5-HT_3 antagonist augmentation can be recommended as an OCD treatment, controlled studies in more diverse populations are needed.

Additional Agents

Other agents, including lithium (McDougle *et al.* 1991; Pigott *et al.* 1991), the benzodiazepines alprazolam (Stein *et al.* 1992) and clonazepam (Crockett *et al.* 2004; Hollander *et al.* 2003c), thyroid hormone (Pigott *et al.* 1991), the tricyclic antidepressant desipramine (Hoehn-Saric *et al.* 2000; Leonard *et al.* 1989, 1991), the glutamate modulator mavoglurant (Rutrick *et al.* 2017), folic acid (Tural *et al.* 2019), and L-methylfolate (Dar *et al.* 2021), have also been tested as potential augmentation agents for OCD. Controlled trials of these medications have not revealed any convincing evidence that they are helpful when added to SRI treatment.

Emerging Combination/Augmentation Pharmacotherapies

Although current evidence-based pharmacotherapies for OCD are effective, some patients will continue to have clinically impairing symptoms despite an adequate dosage and trial duration, and a subset of this group will not achieve response. Given the need for more effective treatments, a variety of novel drugs are being investigated as potential monotherapies or combination/augmentation approaches. None of these agents have established efficacy for treating OCD symptoms, and some (e.g., ketamine) are typically delivered only in specialized settings. However, these approaches may be considered for patients whose symptoms respond poorly to the strategies described earlier.

Glutamate Modulators

Evidence that altered glutamate neurotransmission in the corticostriatal brain circuitry may contribute to OCD symptoms has led researchers to evaluate the use of glutamate modulators to augment SRI response in patients with treatment-resistant OCD (Pittenger *et al.* 2011). This line of research remains preliminary. However, several agents have shown early promise in small trials, as summarized next.

N-Acetylcysteine

N-Acetylcysteine (NAC) is a nutraceutical precursor of the amino acid cysteine that is involved in glutathione synthesis and is used in a variety of clinical situations, including as a mucolytic and to treat acetaminophen overdose (Couto and Moreira 2018). NAC's capacity to modulate glutamate neurotransmission and antioxidant properties led to studies of its potential to augment SRI treatment of OCD. Of the five randomized placebo-controlled NAC augmentation trials that have been conducted, three (two in adult patients [Afshar *et al.* 2012; Sarris *et al.* 2015] and one in children and adolescents [Ghanizadeh *et al.* 2017]) reported that patients receiving NAC augmentation showed modestly greater improvement in OCD symptoms compared with those receiving placebo. Another trial in adults (Paydary *et al.* 2016) found no significant difference in Y-BOCS scores between NAC and placebo, but patients who received NAC were more likely to achieve remission (i.e., Y-BOCS score [?] 16 at trial end). Finally, a study in adults (Costa *et al.* 2017) found no difference between NAC and placebo augmentation of SRI treatment. A recent meta-analysis reported that NAC augmentation showed mild to moderate benefit for OCD symptoms and no increased risk for adverse events compared with placebo (Gadallah *et al.* 2020). NAC dosing in these trials ranged from 600 to 3,000 mg/day, but most participants were treated with a dosage of 2,000-3,000 mg/day.

There remains a need for controlled trials of NAC in larger samples of patients with OCD. Nonetheless, NAC can be obtained without a prescription in the United States, has an excellent safety profile, and increasingly seems to have modest benefit in both adult and pediatric OCD populations when added to SSRIs (Gadallah *et al.* 2020). Given these factors, NAC is a reasonable starting point when considering augmentation with a glutamate modulator, particularly for children and adolescents.

Memantine

Several open-label and controlled trials also support memantine augmentation of SRIs. Memantine, which is FDA approved for treating Alzheimer's disease, is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that may improve OCD symptoms by attenuating excessive glutamate signaling in corticostriatal circuitry (Modarresi *et al.* (2019). Initial open-label trials in both adults and children with OCD found some benefit from memantine augmentation of SSRIs (Aboujaoude *et al.* 2009; Feusner *et al.* 2009; Hezel *et al.* 2009; Rodriguez *et al.* 2016a; Stewart *et al.* 2010). Subsequently, multiple randomized placebo-controlled trials have reported moderate to large benefits from memantine augmentation in adults with OCD (Modarresi *et al.* (2018), including two with response rates of 93% and 100% (Ghaleiha *et al.* (2013; Haghighi *et al.* (2013). Another study found that memantine improved obsessions and compulsions that emerged during manic episodes in adult inpatients with bipolar disorder (Sahraian *et al.* (2017). Most of these studies used a memantine dosage of 20 mg/day. Side effects were generally mild and included fatigue and anxiety (Modarresi *et al.* (2019).

Although a recent meta-analysis supported the benefit of memantine augmentation in OCD (Modarresi *et al.* (2019), an additional randomized placebo-controlled trial in 99 adults with OCD found no difference between memantine and placebo (Farnia *et al.* 2018). Moreover, there are reasons to be skeptical of the large effects for memantine in the abovementioned studies. All four--Ghaleiha *et al.* (2013, Haghighi *et al.* (2013, Modarresi *et al.* (2018, and Sahraian *et al.* (2017)--had small sample sizes (*n* = 38, 29, 30, and 38, respectively) and were conducted in the same geographic region (Iran), which may limit their broader generalizability (Andrade 2019). Larger trials in more diverse populations are needed before memantine augmentation can definitively be considered effective in OCD treatment.

Riluzole

Riluzole is a glutamate modulator primarily used to treat amyotrophic lateral sclerosis and is thought to reduce glutamatergic neurotransmission through several mechanisms, including inhibiting glutamate release, inactivating voltage-gated sodium channels in cortical neurons, blocking GABA reuptake, and facilitating glutamate reuptake (Pittenger *et al.* 2008). A retrospective case series and an open-label trial (both in 13 adults with SSRI-resistant OCD) found that riluzole augmentation reduced OCD symptoms. More recently, two randomized placebo-controlled trials in patients with SSRI-resistant OCD (one in 22 adult outpatients and 11 adult inpatients and another in 59 children) both found no difference in OCD symptom reduction between riluzole and placebo (Grant *et* *al.* 2014; Pittenger *et al.* 2015). However, a third trial in 39 adults with SSRI-resistant OCD found that Y-BOCS scores were significantly more reduced with 8 weeks of riluzole augmentation compared with placebo (Emamzadehfard *et al.* 2016). Troriluzole, a riluzole prodrug, was also recently tested as an augmentation strategy in a large multicenter trial of adults with SRI-resistant OCD. No results are currently published, but press releases indicate that the study did not achieve its primary efficacy endpoint (Biohaven Pharmaceuticals 2020). The current evidence is insufficient to support riluzole augmentation in clinical treatment of OCD.

Topiramate

Topiramate is an antiepileptic drug that, like riluzole, modulates glutamate neurotransmission through several different mechanisms (Pittenger 2015). Two small open-label studies in adults with SSRI-resistant OCD found some benefit from topiramate augmentation (Rubio *et al.* 2006; Van Ameringen *et al.* 2006). Three randomized placebo-controlled trials were subsequently conducted in adults with SSRI-resistant OCD. One trial with 49 patients found significant benefit for topiramate augmentation over placebo (Mowla *et al.* 2010); a second trial with 36 patients reported that topiramate significantly improved compulsions, but not obsessions, compared with placebo (Berlin *et al.* 2011); and finally, a third trial with 38 patients found no difference between topiramate and placebo (Afshar *et al.* 2014). Topiramate was poorly tolerated across all three studies, with a number of participants dropping out due to adverse effects including paresthesias, fatigue, problems with memory and cognition, and kidney stones. Given its poor tolerability and limited data supporting its efficacy, topiramate augmentation cannot currently be recommended in OCD treatment.

Lamotrigine

Lamotrigine is an antiepileptic and mood-stabilizing drug that also has glutamate-modulating properties. Of two case series examining lamotrigine augmentation in patients with SSRI-resistant OCD, one found little evidence of symptomatic improvement over 4 weeks of treatment (Kumar and Khanna 2000), whereas a second found significant improvement in OCD symptoms and quality of life over 16 weeks (Hussain *et al.* 2015). A randomized placebo-controlled trial of lamotrigine augmentation (100 mg/day) in 33 adults with SSRI-resistant OCD found that it significantly improved OCD symptoms versus placebo over 16 weeks of treatment (Bruno *et al.* 2012). A similar trial in 53 adult patients treated for 12 weeks also found significant benefit for lamotrigine over placebo (Khalkhali *et al.* 2016). Lamotrigine was well tolerated in these studies; however, the high placebo response rates in both trials limit the conclusions that can be drawn. Further research in larger samples is needed to establish the efficacy of lamotrigine augmentation in the treatment of adult OCD.

Lamotrigine is FDA approved as a maintenance treatment for pediatric bipolar disorder and might have utility in the treatment of children and adolescents with OCD, but this has yet to be explored.

Gabapentin and Pregabalin

Gabapentin and pregabalin are glutamate modulators commonly used in the treatment of neuropathic pain, alcohol and benzodiazepine addiction, and anxiety. Both inhibit the activity of voltage-dependent calcium channels, leading to reduced glutamatergic neurotransmission, although pregabalin is at least three times more potent than gabapentin (Martinotti 2012). In an open-label study that randomly assigned 40 adults with OCD to either fluoxetine alone or fluoxetine combined with gabapentin, gabapentin augmentation seemed to increase the initial treatment response but performed no better than fluoxetine alone after 8 weeks (Onder *et al.* 2008). Somewhat better results have been achieved with pregabalin. A case series in 12 adults with SRI-resistant OCD found some benefit for pregabalin augmentation (Di Nicola *et al.* 2011). A small open-label trial in 10 adults with SRI-resistant OCD found significant improvement over 8 weeks of pregabalin augmentation (Oulis *et al.* 2011), and a randomized placebo-controlled trial in 56 patients reported that their SRI-resistant symptoms were significantly more reduced with pregabalin augmentation compared with placebo (Mowla and Ghaedsharaf 2020). Although the findings for pregabalin show some promise, there are too few data at this stage to evaluate the efficacy of either of these agents in augmenting SRI treatment of OCD.

Amantadine

Amantadine is an antiviral drug that was historically used for influenza prophylaxis but is now used to improve cognitive functioning in pediatric traumatic brain injury, Alzheimer's dementia, and Parkinson's disease (Grados *et al.* 2015). Mechanistically, amantadine both enhances presynaptic dopamine release and antagonizes the NMDA receptor. Two studies have examined its efficacy in augmenting SRI treatment of OCD. In the first, an open-label trial in eight adults whose OCD was unresponsive to at least one SSRI, patient symptoms improved significantly following 6 weeks of amantadine augmentation (Stryjer *et al.* 2014). The second was a controlled study in which unmedicated adults with moderate to severe OCD (i.e., Y-BOCS scores > 21) were randomly assigned to 12 weeks of fluvoxamine 200 mg/day and either placebo or amantadine 100 mg/day (Naderi *et al.* 2019). OCD symptoms improved in both treatment arms, although the group receiving amantadine augmentation experienced slightly greater reductions in OCD symptoms. However, this effect was small (< 3 points on the Y-BOCS) and of questionable clinical significance. Further research is needed to establish whether amantadine augmentation is truly effective.

Glycine

Glycine, an NMDA receptor agonist and glutamate-modulating amino acid, demonstrated potential as an anticompulsive agent in animal experiments and was subsequently tested in a small controlled trial (Kuygun Karci and Gul Celik 2020). Adult patients with SRI-refractory OCD (n = 24) were randomly assigned to 12 weeks of adjuvant glycine (60 mg/day) or placebo. Although some patients' symptoms improved, there was a high dropout rate in the glycine group because of nausea and complaints

about the taste, and there was no significant difference in outcome between groups (Greenberg *et al.* 2009).

Sarcosine

Sarcosine is an endogenous inhibitor of glycine reuptake that may increase the availability of synaptic glycine and thus enhance glutamate neurotransmission (Bergeron *et al.* 1998). In an open-label trial, 26 adults with OCD were treated with sarcosine flexibly dosed between 500 and 2,000 mg/day. Participants were drug naive (n = 8), free of serotonergic medication for at least 8 weeks (n = 6), or taking an SRI (n = 12); sarcosine was delivered as monotherapy in the former two groups and as an adjuvant in the latter (Wu *et al.* 2011). Although there was significant improvement in OCD symptoms across all groups, there were no between-group differences, and few conclusions can be drawn because of the broad inclusion criteria and lack of placebo control.

Ketamine

The NMDA receptor antagonist ketamine has generated interest in the field of psychiatry, owing to a growing literature suggesting that it can induce rapid-onset, long-lasting antidepressant effects (Kraus *et al.* 2019; Zarate *et al.* 2006). Initial case reports suggested that ketamine might have similar effects on OCD symptoms (Rodriguez *et al.* 2011), but subsequent findings have been mixed. An open-label trial of a single ketamine infusion in 10 adults with OCD found that symptoms of depression, but not OCD, improved over the following 3 days (Bloch *et al.* 2012). In contrast, a randomized controlled crossover trial in which 15 patients received both ketamine and placebo (separated by a week) reported that symptoms improved immediately after ketamine infusion and improvement was maintained in 50% of patients 1 week later (Rodriguez *et al.* 2013). Subsequent case series have examined the use of intranasal ketamine (Adams *et al.* 2017; Rodriguez *et al.* 2017) and attempted to extend the effects of intravenous ketamine with memantine (Rodriguez *et al.* 2016a) and CBT (Adams *et al.* 2017; Rodriguez *et al.* 2016b). In a chart review study of 14 adult inpatients with severe, SRI-unresponsive OCD, Y-BOCS scores decreased by at least 25% in 3 patients who received repeated ketamine dosing (average of 2-3 doses per week over 3 weeks), suggesting that repeated infusions could be helpful for a subset of patients with treatment-resistant symptoms (Sharma *et al.* 2020). Overall, the current data are too limited to fully evaluate ketamine's potential benefit in OCD; controlled studies in larger samples are needed.

Rapastinel (GLYX-13), an NMDA receptor glycine-site partial antagonist thought to have similar properties to ketamine, was also recently tested in a small controlled trial of unmedicated adults with severe OCD (Rodriguez *et al.* 2016c). Whereas ketamine was associated with adverse effects including dissociation, dizziness, nausea, and vomiting, rapastinel was well tolerated in this sample. Although OCD symptoms improved in the initial 3 hours after treatment for a subset of patients, these improvements were not sustained at 1-week follow-up.

Anti-Inflammatories

An expanding literature links inflammation and abnormal immunological function to OCD symptoms (Gerentes *et al.* 2019). Interest in the relationship between autoimmunity and OCD began in the 1990s, with the description of pediatric acute neuropsychiatric disorders associated with streptococcal infection (PANDAS [Swedo *et al.* 1998]), a syndrome in which neuropsychiatric symptoms including tics, obsessions, and compulsions occur suddenly in patients with a history of group A Streptococcus infections. This category has since been subsumed by the umbrella category pediatric acute neuropsychiatric syndrome (PANS), which includes cases of rapid-onset OCD symptoms that are not preceded by infection (Swedo *et al.* 2012). Research has extended the proposed relationship between inflammatory/autoimmune processes and OCD to include adults, with recent data revealing abnormal inflammatory markers in the corticostriatal brain circuitry implicated in OCD (Attwells *et al.* 2017). There have also been several recent trials of anti-inflammatory agents as potential treatments for OCD symptoms.

Minocycline

Minocycline is a tetracycline antibiotic that has garnered interest as a potential OCD treatment due to its combination of anti-inflammatory and glutamate-modulating properties (Rodriguez *et al.* 2010). In an initial open-label trial in nine adults with SRI-resistant OCD, minocycline 200 mg/day was added to ongoing SRI treatment but did not yield significant symptomatic improvement over 12 weeks (Rodriguez *et al.* 2010). In contrast, a randomized controlled trial in which 102 unmedicated adults with OCD were treated with 10 weeks of fluvoxamine 200 mg/day and either minocycline 200 mg/day or placebo reported significantly greater improvement in obsessions, but not compulsions, among those who received minocycline (Esalatmanesh *et al.* 2016). However, the overall benefit of minocycline was quite small, and further research is needed to determine whether this effect can be replicated.

Celecoxib

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits the cyclooxygenase-2 enzyme and is approved in the United States for the treatment of arthritis and other inflammatory conditions (Grassi and Pallanti 2018). Two randomized controlled trials added celecoxib 400 mg/day versus placebo augmentation to ongoing treatment with an SSRI (either fluoxetine 20 mg/day or fluvoxamine 200 mg/day) in adults with OCD; both found greater symptomatic improvement with celecoxib augmentation over placebo across 8 weeks of treatment (Sayyah *et al.* 2011, *n* = 25; Shalbafan *et al.* 2015, *n* = 50). Study design issues, including the low SSRI dosages used and an insufficient treatment period before adding celecoxib, complicate interpretation of these results. Two additional studies of celecoxib augmentation in patients with OCD (one in adults [https://clinicaltrials.gov/study/NCT04786548] and one in children [https://clinicaltrials.gov/study/NCT04673578]) are listed as ongoing on ClinicalTrials.gov but have yet to post results.

Nonsteroidal Anti-Inflammatory Drugs

The role of NSAIDs as a class was examined in a retrospective chart review of 77 children meeting PANS criteria who received these agents for arthritis, pain, or psychiatric symptoms (Spartz *et al.* 2017). Results suggested that neuropsychiatric symptoms improved in roughly a third of patients, with mild gastrointestinal symptoms being the most common side effect. No controlled studies of NSAIDs in the treatment of PANS have been conducted, limiting the conclusions that can be drawn.

Antibiotics

Evidence of an association between bacterial infections and neuropsychiatric symptoms (including OCD symptoms) led to the hypothesis that antibiotics might reduce OCD symptoms in these cases (Burchi and Pallanti 2018). To date, only three trials have tested this possibility, with mostly negative results. The first was a randomized double-blind, placebo-controlled crossover study in 37 children with PANDAS, which did not show any benefit to OCD symptoms or tics with 4 months of penicillin prophylaxis compared with placebo (Garvey *et al.* 1999). The second was a randomized double-blind, placebo-controlled trial of azithromycin in 31 children with PANS (of whom 19 met PANDAS criteria) over 4 weeks (Murphy *et al.* 2017). The investigators found that CY-BOCS scores did not differ between the azithromycin and placebo groups, although overall severity on the Clinical Global Impression Scale was significantly lower among those who received azithromycin. Finally, a third study evaluated the effects of 30 days of treatment with the cephalosporin antibiotic cefdinir in 20 children with recent-onset OCD symptoms or tics, who were not required to have a history of infection or meet PANS criteria. The investigators found no differences in either OCD symptoms or tics among those who received cefdinir versus placebo (Murphy *et al.* 2015). These study results are challenging to interpret, considering their small size and the heterogeneity of their associated populations and designs. Although further study is warranted, the current literature provides little evidence that antibiotics are effective in treating PANS or OCD symptoms.

Opiates

A few studies have examined the use of modulators of the m opioid receptor in patients with SRI-resistant OCD. In one open-label trial, seven adults with OCD refractory to SRIs underwent a medication washout and were then treated with tramadol ([?] 400 mg/day). OCD symptoms decreased by 26% over the 6-week trial (Shapira *et al.* 1997). A later study evaluated the effects of augmenting SRIs with morphine, which lacks tramadol's serotonin/norepinephrine reuptake inhibition and is 6,000 times more potent at the m opioid receptor (Koran *et al.* 2005a). In a within-subjects design, 23 adults with SRI-refractory OCD completed three 2-week study blocks in which they received once-weekly oral morphine (15-45 mg), lorazepam (0.5-2 mg), or placebo. Morphine led to significantly greater improvement in OCD symptoms than either lorazepam or placebo (Koran *et al.* 2005a). Finally, a randomized placebo-controlled trial examined the effects of augmenting SRIs with the partial m opioid receptor agonist buprenorphine. In 43 adults whose OCD symptoms were SRI unresponsive, buprenorphine augmentation led to a faster decline in symptoms than placebo but did not differ in its effect on Y-BOCS scores over the course of 12 weeks (Ahmadpanah *et al.* 2017). The findings for each of these opiates are intriguing, but they require rigorous testing in larger trials before any conclusions can be drawn.

Tolcapone

Tolcapone is a selective, reversible inhibitor of the enzyme catechol O-methyltransferase that is FDA approved as an adjuvant to levodopa-carbidopa therapy for Parkinson's disease (Enna and Bylund 2011). Given its capacity to enhance dopaminergic signaling, a recent randomized double-blind, placebo-controlled crossover trial examined the effects of 2 weeks of tolcapone treatment in 20 adults with OCD (Grant *et al.* 2021b). Tolcapone led to modest but significant improvements in OCD symptoms over placebo, supporting its further investigation by future studies in patients with OCD.

Psilocybin

In the past decade, there has been a resurgence of interest in the therapeutic applications of psychedelics for various psychiatric conditions (Lieberman and Shalev 2016). In OCD, the serotonergic psychedelic psilocybin has garnered particular attention (Wilcox 2014) and so far is the only psychedelic drug to receive substantial research attention. Psilocybin is a component of various fungal species, including the *Psilocybe cubensis* mushroom (Halberstadt *et al.* 2018). When ingested, psilocybin is converted into the lipid-soluble psilocin, which rapidly crosses the blood-brain barrier and is thought to be responsible for its psychoactive effects (Jacobs 2020). Psilocin is active at a number of receptors in the brain but has high affinity for 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_{2C}$ receptors (Halberstadt *et al.* 2018). The characteristic psychedelic effects of psilocybin include altered perception and cognition and are thought to be due to 5-HT$_{2A}$ agonism in particular (Carhart-Harris *et al.* 2011). Psilocybin has also been associated with increased expression of brain-derived neurotrophic factor (which is thought to play a role in neurogenesis and have neuroprotective effects), modulation of glutamate signaling, and transient increases in global connectivity throughout the brain, all of which are hypothesized to relate to its purported therapeutic benefits (Jacobs 2020).

Psilocybin was tested in patients with OCD in a small open-label trial in 2006 (Moreno *et al.* 2006). Nine adults with OCD received increasing single doses of psilocybin ([?] 300 mcg/kg), each separated by at least a week, with a single low dose (25 mcg/kg) administered at a random time point after the first dose. Participants were monitored over the next 8 hours and again at 24 hours postingestion. Psilocybin was well tolerated, and all participants reported symptomatic improvement after receiving psilocybin.

However, the effects were not dose dependent, and, in fact, four participants reported substantial improvement after receiving the 25-mcg/kg dose, which was intended to be a placebo comparator (Moreno *et al.* 2006). Although intriguing, this study was limited by design issues, including a small sample size and lack of a true placebo. There is also debate concerning how best to deliver psilocybin, with some suggesting that its effects may depend on facilitating psychotherapy (e.g., by enhancing openness to change and/or acceptance of emotional experience) and others stating that its effects are primarily pharmacological in nature (Jacobs 2020).

Agomelatine

Agomelatine is a novel medication that is approved as an antidepressant in Europe and Australia but is not currently FDA approved in the United States. Agomelatine acts as both an antagonist of the 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors and an agonist of the melatonin MT$_1$ and MT$_2$ receptors; synergy between these effects is also thought to increase dopamine and norepinephrine levels in the prefrontal cortex and to promote cortical and hippocampal expression of brain-derived neurotrophic factor (Martinotti *et al.* 2016). This unique mechanistic profile has garnered greater interest in agomelatine as a possible treatment for sleep disturbances that occur in the setting of psychiatric illness.

Particular interest in agomelatine's potential role in treating OCD has recently developed in light of evidence that circadian rhythm abnormalities are much more common in

OCD than in the general population (estimated range, 17%-42% vs. 1%-10%, respectively [Nota *et al.* 2015]) and that these abnormalities are correlated with OCD symptom severity (Mukhopadhyay *et al.* 2008; Turner *et al.* 2007) and responsiveness to treatment (Donse *et al.* 2017). Although controlled studies have not been conducted, a recent case series including 10 adults with OCD who were treated with agomelatine showed that symptoms improved in all 7 patients who reported pretreatment sleep disturbances, with a reduction in Y-BOCS scores ranging from 46% to 90%. In contrast, Y-BOCS scores showed little to no change among those who did not report sleep disturbances (Coles and Goodman 2020). Although they are too preliminary to support clinical use at this stage, these encouraging findings suggest that controlled trials of agomelatine for treating individuals with OCD and comorbid sleep disturbances are warranted.

Nutraceuticals

Nutraceuticals (i.e., food products, herbs, and other dietary supplements thought to have health benefits) with serotonergic, antioxidant, anti-inflammatory, and/or glutamate-modulating properties have also been evaluated as either standalone or adjuvant therapies for treating OCD symptoms (Kuygun Karci and Gul Celik 2020). Agents tested to date and relevant information from the studies in which they were evaluated are summarized in Table 52-3. Of the agents tested, the most promising may be the dietary elements zinc and selenium--the serum levels of which were found to be lower in adults with OCD (Ozdemir *et al.* 2009; Shohag *et al.* 2012). Two augmentation studies found small but significant reductions in Y-BOCS scores when zinc (Sayyah *et al.* 2012a) and selenium (Sayyah *et al.* 2018) were added to ongoing SRI treatment compared with placebo. A recent open-label study reported on a nutraceutical formulation that included both zinc and selenium, along with NAC, L-theanine, and pyridoxal 5'-phosphate, in 20 adults with OCD unresponsive to prior SRI treatment. The combined formula containing multiple nutraceuticals as an adjuvant to SRI treatment was associated with a significant reduction in Y-BOCS scores over 20 weeks, although response was greatest among those with less severe symptoms at baseline and was minimal among those with more severe symptoms (Sarris *et al.* 2022).

TABLE 52-3. Nutraceuticals tested in patients with obsessive-compulsive disorder

Agent	Putative mechanism	Studies	Design	Sample	Key findings
Myoinositol	Thought to modulate 5-HT reuptake and increase 5-HT receptor density (Kuygun Karci and Gul Celik 2020)	1) Carey *et al.* 2004	1) 6-week randomized double-blind, placebo-controlled crossover study of inositol monotherapy	1 and 2) Adults with OCD (*n* = 13 and 14)	1) Significantly greater reduction in Y-BOCS scores with inositol (18 g) over placebo
		2) Fux *et al.* 1996	2) 12-week open-label trial of inositol monotherapy	2) Significant reduction in Y-BOCS over 12 weeks of inositol (18 g) treatment	
		3) Fux *et al.* 1999	3) 6-week randomized double-blind, placebo-controlled crossover study of inositol augmentation of SRI	3 and 4) Adults with OCD unresponsive to SRIs (*n* = 10, both studies)	3) No between-group difference in Y-BOCS
4) Seedat and Stein 1999	4) 6-week open-label trial of inositol augmentation of SRI	4) No significant change in Y-BOCS or Clinical Global Impression Scale scores			
5-Hydroxy-tryptophan	Nonessential amino acid; precursor to	Yousefzadeh *et al.* 2020	Randomized double-blind, placebo-	Adults with OCD (*n* = 60)	Small but significant Y-BOCS reduction

Note. 5-HT = 5-hydroxytryptamine (serotonin); MAO = monoamine oxidase; NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Agent	**Putative mechanism**	**Studies**	**Design**	**Sample**	**Key findings**
	5-HT (Kuygun Karci and Gul Celik 2020)		controlled trial of 5-hydroxytryptophan augmentation (200 mg/day)		for 5-hydroxytryptophan vs. placebo augmentation of fluvoxamine (20 mg/day for 4 weeks before study, then [?] 60 mg/day)
Limitations: submaximal fluvoxamine dosage, inadequate fluvoxamine pretreatment					
St. John's wort (*Hypericum perforatum*)	Inhibition of MAO A/B and of 5-HT, norepinephrine, and dopamine reuptake (Camfield *et al.* 2011)	1) Kobak *et al.* 2005	1) 12-week open-label trial of St. John's wort monotherapy (900 mg/day)	1) Adults with OCD (*n* = 12)	1) Significant Y-BOCS reduction over 12 weeks
2) Taylor and Kobak 2000	2) 12-week randomized double-blind, placebo-controlled trial of St. John's wort monotherapy (600-1,800 mg/day)	2) Adults with OCD (*n* = 60)	2) No difference in Y-BOCS for St. John's wort vs. placebo		

Note. 5-HT = 5-hydroxytryptamine (serotonin); MAO = monoamine oxidase; NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Agent	**Putative mechanism**	**Studies**	**Design**	**Sample**	**Key findings**
Saffron (*Crocus sativus* L.) and crocin (active component of saffron)	Poorly understood; may have anxiolytic, antidepressant, and/or neuroprotective properties (Ayati *et al.* 2020)	1) Esalatmanesh *et al.* 2017	1) 10-week randomized controlled trial of saffron (30 mg/day) vs. fluvoxamine (100 mg/day)	1) Unmedicated adults with mild to moderate OCD (Y-BOCS range, 12-21; *n* = 50)	1) Y-BOCS decreased in both groups; no between-group differences
		2) Kazemi *et al.* 2021	2) 8-week randomized controlled trial of crocin (15 mg) vs. fluoxetine (20 mg)	2) Unmedicated adults with mild to moderate OCD (Y-BOCS range, 12-25; *n* = 50)	2) Y-BOCS decreased in both groups; no between-group differences
			Limitations: lack of placebo control, inadequate SRI dosage and trial duration		
Ashwaganda *(Withania somnifera)*	Properties may include anti-inflammatory and antioxidant effects, cholinesterase inhibition (Chengappa *et al.* 2013)	Jahanbakhsh *et al.* 2016	6-week randomized double-blind, placebo-controlled trial of ashwaganda extract (120 mg/day) augmentation of ongoing SSRI treatment	Adults with OCD currently taking an SSRI (*n* = 30)	Significantly greater reduction in Y-BOCS scores for ashwaganda vs. placebo (12 vs. 8 points, respectively)
Limitations: small sample, short trial duration; baseline Y-BOCS was 8					

Note. 5-HT = 5-hydroxytryptamine (serotonin); MAO = monoamine oxidase; NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Agent	Putative mechanism	Studies	Design	Sample	Key findings
points lower in ashwaganda group than in placebo group					
Milk thistle *(Silybum marianum)*	Poorly understood; may have antioxidant and anti-inflammatory properties; increases cortical serotonin and/or MAO inhibition (Kuygun Karci and Gul Celik 2020)	Sayyah *et al.* 2010	8-week randomized controlled trial of milk thistle extract (600 mg/day) vs. fluoxetine (30 mg/day)	Unmedicated adults with OCD (*n* = 35)	Y-BOCS scores decreased in both groups; no between-group differences
Limitations: small sample, inadequate fluoxetine dosage and trial duration					
Valerian root (*Valeriana officinalis* L.)	Poorly understood; may have GABAergic properties (Kuygun Karci and Gul Celik 2020)	Pakseresht *et al.* 2011	8-week randomized double-blind, placebo-controlled trial of valerian extract (675 mg/day) vs. placebo	Unmedicated adults with OCD (*n* = 31)	Y-BOCS scores decreased in both groups; small but statistically significant increase in improvement for valerian vs. placebo Somnolence was greater in valerian group
Limitations: small sample					

Note. 5-HT = 5-hydroxytryptamine (serotonin); MAO = monoamine oxidase; NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Agent	Putative mechanism	Studies	Design	Sample	Key findings
size, short trial duration, lack of comparison to evidence-based treatment, clinical meaningfulness of small treatment effect unclear					
Borage (*Echium amoenum*)	Poorly understood; may have anxiolytic and/or antidepressant properties (Sarris *et al.* 2011)	Sayyah *et al.* 2009	6-week randomized double-blind, placebo-controlled trial of borage extract (500 mg/day) vs. placebo	Unmedicated adults with OCD (*n* = 44)	Y-BOCS scores decreased in both groups; small but statistically significant increase in improvement for borage vs. placebo
Limitations: small sample size, short trial duration, lack of comparison to evidence-based treatment, clinical meaningfulness of small treatment effect unclear					
Zinc	Dietary element; serum levels may be decreased in OCD	Sayyah *et al.* 2012a	6-week randomized double-blind, placebo-controlled trial of zinc (440 mg/day) or placebo	Unmedicated adults with OCD (*n* = 23)	Y-BOCS scores decreased in both groups; small but statistically significant increase in improvement for

Note. 5-HT = 5-hydroxytryptamine (serotonin); MAO = monoamine oxidase; NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Agent	**Putative mechanism**	**Studies**	**Design**	**Sample**	**Key findings**
	(Shohag *et al.* 2012)		augmentation of fluoxetine (20 mg/day)		zinc vs. placebo augmentation
Limitations: small sample size, short trial duration, clinical meaningfulness of small treatment effect unclear, no control for dietary sources of zinc					
Selenium	Dietary element; serum levels may be decreased in OCD (Ozdemir *et al.* 2009)	Sayyah *et al.* 2018	6-week randomized double-blind, placebo-controlled trial of selenium (200 mg/day) or placebo augmentation of ongoing SRI treatment	Adults with OCD unresponsive to ongoing SSRI treatment (*n* = 32)	Y-BOCS scores decreased in both groups; small but statistically significant increase in improvement for selenium vs. placebo augmentation
Limitations: small sample size, short trial duration, clinical meaningfulness of small treatment effect unclear, no control for dietary sources of selenium					

Note. 5-HT = 5-hydroxytryptamine (serotonin); MAO = monoamine oxidase; NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Agent	Putative mechanism	Studies	Design	Sample	Key findings
Nutraceutical combination	Multiple	Sarris *et al.* 2022	20-week open-label trial of a nutraceutical formulation containing NAC, L-theanine, zinc, magnesium, pyridoxal 5'-phosphate, and selenium as augmentation of ongoing SSRI treatment	Adults with OCD unresponsive to ongoing SSRI treatment (*n* = 20)	Y-BOCS scores decreased by a mean of 7.13 over the course of the trial; 23% of participants were considered responders (i.e., Y-BOCS decrease [?] 35%) Effects were greatest in those with lowest baseline Y-BOCS scores; minimal response in those with more severe symptoms
Limitations: small sample size, high dropout rate, lack of placebo control					

Note. 5-HT = 5-hydroxytryptamine (serotonin); MAO = monoamine oxidase; NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

These findings should be considered preliminary at best, considering that all of the studies included small samples and most had significant design flaws that limit their interpretation. As a result, none of the nutraceuticals summarized here can be recommended for patients with OCD in most clinical situations. Nonetheless, nutraceuticals are often easier to access and present relatively few risks compared with prescription medications, and they are thus of great interest to patients and clinicians alike. Further research in well-designed controlled trials is warranted to determine whether any of these agents is effective in patients with OCD.

Pharmacological Augmentation of Exposure and Ritual Prevention Cognitive-Behavioral Therapy

CBT consisting of exposure and ritual prevention (EXRP) is well established as a treatment for OCD, and the strong evidence supporting its efficacy has led to its recommendation as a first-line therapy (Foa *et al.* 1984; Franklin *et al.* 2000; Koran *et al.* 2007; Simpson *et al.* 2013). Nonetheless, fewer than half of patients who receive a full course of EXRP will achieve remission (Farris *et al.* 2013; Simpson *et al.* 2006, 2008, 2021). Recognizing this limitation, there have been a variety of attempts to use medications to enhance the effectiveness of EXRP. The agents that have been tested generally affect neurocognitive functions that are supported by CBT and the brain circuits that subserve them (Patel *et al.* 2021). These functions include fear processing (e.g., extinction learning and recall, safety learning, memory reconsolidation [Fullana *et al.* 2020]) and cognitive control (McTeague *et al.* 2017; Wheaton *et al.* 2016). Studies of agents tested as potential pharmacological enhancers of CBT are summarized next.

D-Cycloserine

D-Cycloserine is a partial NMDA receptor agonist shown in animal studies to enhance both synaptic plasticity and the associative learning processes involved in fear extinction (Kaplan and Moore 2011). Interest in the potential of D-cycloserine to facilitate human fear extinction increased after an initial proof-of-concept study in patients with height phobia reported that D-cycloserine improved outcomes when added to exposure treatment (Ressler *et al.* 2004). Since then, at least eight randomized controlled trials have compared EXRP monotherapy against EXRP in combination with D-cycloserine among either adults or children with OCD. Of the four adult studies, two found that D-cycloserine increased the initial response rate but ultimately did not lead to greater symptomatic improvement than EXRP alone (Kushner *et al.* 2007; Wilhelm *et al.* 2008), whereas three others found no benefit from D-cycloserine augmentation (Andersson *et al.* 2015; de Leeuw *et al.* 2017; Storch *et al.* 2007). Similarly, one study of D-cycloserine augmentation in children with treatment-resistant OCD found that it improved EXRP outcomes at 1-month follow-up (Farrell *et al.* 2013) but showed no difference at 3-month follow-up, whereas two other studies in this population found no between-group differences in outcome (Mataix-Cols *et al.* 2014; Storch *et al.* 2016). More recently, four separate meta-analyses found that D-cycloserine augmentation had minimal effects on OCD symptoms (Burkner *et al.* 2017; Mataix-Cols *et al.* 2017; McGuire *et al.* 2017; Xia *et al.* 2015). Secondary analyses of pooled data from 21 studies of D-cycloserine augmentation of exposure treatment for OCD and other conditions suggest that inconsistencies in the timing and number of doses used in these studies may contribute to the lack of observed efficacy, suggesting that further research is warranted (Rosenfield *et al.* 2019). Nonetheless, the current literature provides insufficient support to recommend D-cycloserine augmentation of EXRP in clinical practice.

Ketamine

Rodent studies suggesting that ketamine can promote synaptic plasticity (Gideons *et al.* 2014; Liu *et al.* 2012) and facilitate extinction learning (Duman 2014) prompted a small open-label trial of its use to augment EXRP in adults with OCD. Unmedicated adults with OCD (*n* = 10) received intravenous ketamine, followed by 10 EXRP sessions delivered in the 2-week interval after ketamine administration when its effects on fear extinction are thought to be greatest. Results suggested that ketamine rapidly improved obsessions, and that its combination with EXRP had better efficacy than either

treatment alone (Rodriguez *et al.* 2016b). Although intriguing, these preliminary findings have yet to be evaluated in randomized controlled trials.

Cannabinoids

Agents that modulate the brain's endocannabinoid system (i.e., cannabinoids) have also been tested as potential facilitators of exposure-based treatment, including in OCD (Kayser *et al.* 2019). The idea that cannabinoids might enhance EXRP treatment stems from convergent preclinical evidence that these agents can attenuate excessive threat responding (Phan *et al.* 2008; Rabinak *et al.* 2020), facilitate extinction learning and/or recall (Hammoud *et al.* 2019; Rabinak *et al.* 2013, 2014, 2018), and/or promote an appropriate balance between goal-directed and habitual behaviors (Gianessi *et al.* 2020, 2022; Gremel *et al.* 2016). Cannabinoid augmentation of EXRP was recently investigated in a small trial in 11 unmedicated adults with OCD (Kayser *et al.* 2020). Participants were randomly assigned to 4 weeks of either monotherapy with nabilone (a synthetic analog of D-9-tetrahydrocannabinol, the primary psychoactive component of the cannabis plant and a partial agonist at the cannabinoid CB_1 receptor) or nabilone combined with nine sessions of EXRP. A separate group of patients received 4 weeks of EXRP alone. Participants who received nabilone alone showed little improvement, whereas those who received nabilone with EXRP improved nearly twice as much as those in the comparison sample who received EXRP alone (Kayser *et al.* 2020). As with ketamine, nabilone augmentation of EXRP needs to be evaluated in larger randomized controlled trials before it can be recommended in clinical practice. Nabilone's engagement with the fear network and its other putative mechanistic targets must also be confirmed in mechanistic studies.

Neuromodulation and Neurosurgical Approaches

Neuromodulation involves delivering targeted stimulation to key brain regions in order to modulate activity within distinct neural circuits. These approaches, developed and refined over the past two decades, may offer greater specificity than most pharmacotherapies. The intensity of neuromodulation can be adjusted in many cases to enable flexible "dosing," while the reversibility of these approaches may mitigate their potential for adverse effects (Bais *et al.* 2014). Although a detailed discussion of these approaches is beyond the scope of this chapter, we will provide an overview of key findings regarding the safety and efficacy of neuromodulation in OCD treatment.

Electroconvulsive Therapy

Although electroconvulsive therapy was widely used in OCD treatment until the mid-1980s, it has fallen out of favor due to safety concerns and equivocal data regarding efficacy (Bais *et al.* 2014). Several case reports and case series suggest that electroconvulsive therapy may benefit selected patients with severe, treatment-resistant OCD symptoms (often with comorbid depression), but this has not been tested in controlled trials (Dos Santos-Ribeiro *et al.* 2018). As a result, electroconvulsive therapy is rarely used to treat OCD in clinical practice today and is recommended only for patients with comorbid conditions that are likely to be responsive (e.g., severe depression).

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive technique in which pulses of electricity are passed through a coil placed over the head, inducing a magnetic field that modulates excitability within targeted cortical regions (Bais *et al.* 2014). The degree of excitability varies with the frequency of the stimulation, with high-frequency stimulation (5-20 Hz) increasing and low-frequency stimulation (0-5 Hz) decreasing neuronal activity. Because TMS only transiently alters activity in the targeted brain circuits, repetitive administration (i.e., repetitive transcranial magnetic stimulation [rTMS]) is required to produce longer-term effects (Bais *et al.* 2014).

rTMS studies have focused on stimulating brain regions and circuits in which abnormal function has been linked to OCD symptoms. These include the supplemental motor area (SMA), the dorsolateral prefrontal cortex (dlPFC), and the orbitofrontal cortex (OFC). The SMA is involved in higher-order motor control and coordinating sequential motor actions and is thought to be hyperactive in OCD, which may contribute to compulsive behaviors (Mantovani *et al.* 2010). The dlPFC is broadly involved in executive functions that coordinate goal-directed behaviors, which include working memory, planning, and control over affective, attentional, and sensorimotor processes (Shephard *et al.* 2021). dlPFC hypoactivity is thought to contribute to clinical impairments seen in patients with OCD, including pathological doubt, compulsive checking, and deficient emotion regulation. The OFC is thought to moderate reward-associated learning and decision-making. Aberrant OFC activity during reward processing is thought to underlie aberrant reward processing that has been observed in patients with OCD (Kaufmann *et al.* 2013) and may contribute to compulsive behaviors. Table 52-4 summarizes the results of rTMS studies targeting each of these regions. Overall, only OFC-targeted rTMS has consistently been found to reduce OCD symptoms in controlled studies; results from trials targeting the dlPFC and SMA have been mixed.

TABLE 52-4. Neuromodulation and neurosurgical approaches

Role in treatment	Clinical considerations	Supporting research
Electroconvulsive therapy (ECT)		
Not recommended in most clinical situations	Case reports suggest some potential benefit for patients with OCD and severe comorbid depression, but this has not been tested in controlled trials.	Bais *et al.* 2014
ECT is generally not recommended in OCD because of the lack of evidence of efficacy and risk for impaired cognition and other side effects.	Dos Santos-Ribeiro *et al.* 2018	
Transcranial magnetic stimulation (TMS)		

Note. DBS = deep brain stimulation; dTMS = deep transcranial magnetic stimulation; OFC = orbitofrontal cortex; SMA = supplemental motor area; SRI = serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Role in treatment	Clinical considerations	Supporting research
May have some benefit in patients with symptoms unresponsive to > 1 SRI trial	A noninvasive technique in which a magnetic field modulates excitability within targeted brain regions.	Carmi *et al.* 2019
	Only dTMS has consistently shown benefit for OCD and is FDA approved.	McCathern *et al.* 2020
	dTMS targeting the medial prefrontal cortex and dorsal anterior cingulate cortex was shown to be more effective than sham TMS in controlled studies when paired with personalized symptom provocations; there is currently no evidence that dTMS is effective if not delivered alongside provocations.	Roth *et al.* 2021
Side effects include localized scalp discomfort, muscle twitches, lightheadedness, and headaches; serious side effects are rare and include seizures and hearing loss (can be mitigated by using earplugs).		
Neurosurgery		
As a last resort in severe, treatment-refractory cases	In a systematic review, ablative procedures (e.g., cingulotomy and anterior capsulotomy) led to improvement in 25%-50% of patients with severe, treatment-refractory OCD.	Denys *et al.* 2010
	Ablative procedures were generally well tolerated but should be pursued only as a last resort because of their irreversible nature.	Hageman *et al.* 2021
	DBS involves implanting a small electrode in the brain, usually in the region of the bed nucleus of the stria terminalis and nucleus accumbens.	Luyten *et al.* 2016
	DBS may be a potentially reversible alternative, and was recently granted a humanitarian exemption by the FDA.	Pepper *et al.* 2015
DBS led to an average acute Y-BOCS score reduction of 40% among patients with treatment-refractory OCD in recent controlled trials, but its long-term effects remain unclear.	Wu *et al.* 2021	
Other neuromodulation approaches		

Note. DBS = deep brain stimulation; dTMS = deep transcranial magnetic stimulation; OFC = orbitofrontal cortex; SMA = supplemental motor area; SRI = serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Role in treatment	**Clinical considerations**	**Supporting research**
Current evidence insufficient to recommend in clinical practice	Transcranial direct current stimulation to the SMA and OFC showed promise in early trials; transcranial alternate current stimulation is also under investigation.	da Silva *et al.* 2021
	Magnetic seizure therapy, in which magnetic fields are used to induce localized seizure activity, was not shown to be effective in a small study.	Germann *et al.* 2021
	A small case series suggested that ultrasound capsulotomy may be a noninvasive alternative to ablative neurosurgery, but controlled studies are needed.	Gowda *et al.* 2019
	Tang *et al.* 2021	

Note. DBS = deep brain stimulation; dTMS = deep transcranial magnetic stimulation; OFC = orbitofrontal cortex; SMA = supplemental motor area; SRI = serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Recently, more elaborate coils have been developed that can generate magnetic pulses over a larger area and with deeper penetrance. Deep transcranial magnetic stimulation (dTMS) uses this technology to stimulate deeper regions of the brain, including the medial prefrontal cortex, which is involved in emotion regulation and top-down behavioral control, and the anterior cingulate cortex, which contributes to several functions that are impaired in OCD (including error monitoring, conflict resolution, and integrating motivation and emotion with movement). In a pivotal early trial involving 11 sites, 99 adults with OCD who previously responded poorly to SSRIs or CBT received 6 weeks of daily treatment with either high-frequency dTMS targeting the medial prefrontal cortex and dorsal anterior cingulate cortex or sham dTMS. Critically, personalized symptom provocations (e.g., encouraging a participant with contamination fears to think about a dirty door handle) were delivered shortly before each dTMS session in order to activate the relevant brain circuitry. dTMS treatment led to a significantly greater response rate compared with sham treatment (38.1% vs. 11.0%, respectively), an effect that was sustained at 1-month follow-up (Carmi *et al.* 2019). Based on these findings, dTMS received FDA clearance for its use to treat OCD symptoms in August 2018, and remains the only neuromodulatory approach to attain such clearance. Subsequently, a multicenter study including 219 adults with OCD who were recruited from 22 community sites and were treated with the above protocol found that 58% of patients experienced a Y-BOCS score reduction of at least 30% after 29 dTMS sessions (Roth *et al.* 2021).

Across these studies, both rTMS and dTMS were generally well tolerated. Common side effects included localized scalp discomfort, muscle twitches, lightheadedness, and headaches. More serious concerns include hearing loss (although this is preventable by using earplugs) and seizures (McCathern *et al.* 2020).

Neurosurgery

Between 10% and 40% of patients with OCD will continue to have severe symptoms despite receiving evidence-based treatments (Fineberg *et al.* 2020). For individuals with intractable OCD symptoms, neurosurgery may be considered as a treatment of last resort. Ablative procedures and deep brain stimulation (DBS) are the two most researched techniques and are typically delivered in combination with medications and/or CBT.

Cingulotomy and anterior capsulotomy are ablative procedures that have been used to treat refractory OCD for more than 50 years. A systematic review of 10 studies including 193 patients concluded that both techniques were effective, leading to significant improvement in 25%-50% of patients (Pepper *et al.* 2015). Although these procedures were reasonably well tolerated, the rates of serious or permanent adverse events were high (5.2% of patients who received cingulotomy and 21.4% of those who received anterior capsulotomy).

DBS has shown promise as a potentially reversible alternative to ablative procedures and, as of 2009, has received a humanitarian exemption from the FDA permitting its use to treat patients with refractory OCD (Wu *et al.* 2021). DBS for OCD typically involves implanting an electrode in the vicinity of the ventral anterior capsule and ventral striatum, which includes the nucleus accumbens and bed nucleus of the stria terminalis. Open-label studies (de Koning *et al.* 2016) and two blinded randomized controlled trials (Denys *et al.* 2010; Luyten *et al.* 2016) found substantial acute improvement among patients with treatment-refractory OCD who received DBS, with Y-BOCS scores decreasing by nearly 40%. However, the long-term effects of DBS remain unknown. Although DBS's reversibility is an advantage over ablative procedures, a recent meta-analysis found that DBS and ablative procedures had similar efficacy. Increased impulsivity was also a more common side effect with DBS than with ablative procedures (Hageman *et al.* 2021). Given the limited number of trials and small samples that have been used to date, neurosurgery is still considered an experimental treatment by most guidelines (Wu *et al.* 2021), and its use should be reserved for only the most severe cases.

Emerging Neuromodulation Techniques

The surge in neuromodulation research over the past few years has included studies of several novel techniques in patients with OCD. These approaches are summarized in Table 52-4. Transcranial electric current stimulation, which includes transcranial direct current stimulation and transcranial alternating current stimulation, involves applying a weak electric current to targeted brain regions through an anode and a cathode placed on the scalp. Transcranial direct current stimulation applied to the SMA and OFC has shown early promise for treating OCD in small controlled trials (da Silva *et al.* 2021; Gowda *et al.* 2019), although interpreting these findings is difficult given inconsistencies in the transcranial direct current stimulation protocol used. Magnetic seizure therapy, a therapeutic strategy similar to electroconvulsive therapy, involves applying magnetic stimulation to the brain to induce a generalized seizure. A small trial in 10 patients did not find magnetic seizure therapy to be effective for OCD symptoms (Tang *et al.* 2021). Ultrasound capsulotomy is a novel procedure in which focused ultrasound is used to lesion a small portion of the internal capsule. A recent case series suggests that ultrasound capsulotomy may be an alternative to ablative neurosurgery for some patients with treatment-refractory OCD (Germann *et al.* 2021). However, studies to optimize the procedures and targets involved are needed before ultrasound capsulotomy can be used outside of research settings.

Treatment Algorithms

As reviewed in this chapter, clinical research over the past decade has revealed a variety of new approaches to pharmacological treatment of OCD. Among these agents, SSRIs remain the first-line treatment (alongside EXRP), given the robust evidence supporting their safety and efficacy. However, only a minority of patients with OCD will achieve a complete response to an initial SSRI trial, even after optimizing the dosage and duration (Farris *et al.* 2013). In this situation, it is often reasonable to switch to another SSRI or to clomipramine. Options for patients whose symptoms do not respond to multiple SRI trials include switching to another serotonergic drug (e.g., venlafaxine, mirtazapine) or augmenting with another medication (e.g., an antipsychotic, a glutamate modulator, a stimulant). When symptoms persist despite these interventions, consulting with an expert in OCD treatment is advisable. Treatment options at this stage may include residential treatment, experimental medications (e.g., ketamine), or neuromodulation approaches (e.g., dTMS). Finally, in severe, treatment-refractory cases of OCD, neurosurgical approaches are available as a last resort. The above-described treatment algorithm is summarized in Figure 52-1.

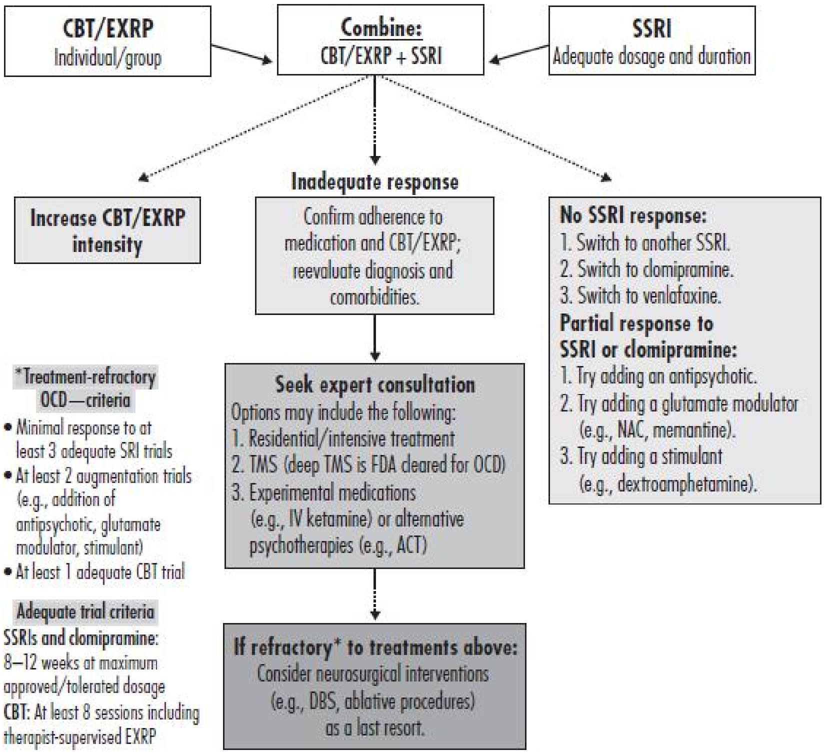
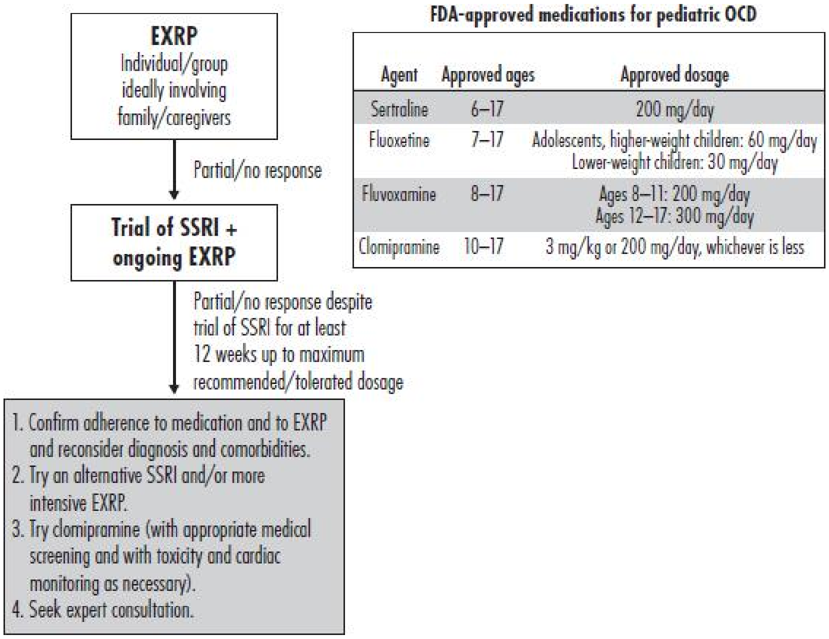

CBT/EXRP
Individual/group
Combine:
CBT/EXRP + SSRI
SSRI
Adequate dosage and duration
Inadequate response
Increase CBT/EXRP intensity
Confirm adherence to medication and CBT/EXRP; reevaluate diagnosis and comorbidities.
No SSRI response:
1. Switch to another SSRI.
2. Switch to clomipramine.
3. Switch to venlafaxine.
Partial response to SSRI or clomipramine:
1. Try adding an antipsychotic.
2. Try adding a glutamate modulator (e.g., NAC, memantine).
3. Try adding a stimulant (e.g., dextroamphetamine).
*Treatment-refractory OCD—criteria
• Minimal response to at least 3 adequate SRI trials
• At least 2 augmentation trials (e.g., addition of antipsychotic, glutamate modulator, stimulant)
• At least 1 adequate CBT trial
Adequate trial criteria
SSRIs and clomipramine: 8–12 weeks at maximum approved/tolerated dosage
CBT: At least 8 sessions including therapist-supervised EXRP
Seek expert consultation
Options may include the following:
1. Residential/intensive treatment
2. TMS (deep TMS is FDA cleared for OCD)
3. Experimental medications (e.g., IV ketamine) or alternative psychotherapies (e.g., ACT)
If refractory* to treatments above:
Consider neurosurgical interventions (e.g., DBS, ablative procedures) as a last resort.

FIGURE 52-1. Treatment algorithm for OCD in adults.

ACT = Acceptance and Commitment Therapy; CBT = cognitive-behavioral therapy; DBS = deep brain stimulation; EXRP = exposure and response/ritual prevention; NAC = *N*-acetylcysteine; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TMS = transcranial magnetic stimulation.

The majority of the treatment studies conducted thus far (and reviewed in this chapter) have involved adults. However, epidemiological studies suggest that the onset of OCD symptoms occurs before age 19 years in approximately 50% of patients with OCD and before age 14 years in around 25% (Ruscio *et al.* 2010). Treatment of children and adolescents with OCD presents a clinical challenge because of the limited data available and increased concern for adverse medication effects in pediatric patients, and thus requires a different approach (Figure 52-2). Given these concerns and the strong support for the safety and efficacy of CBT for children and adolescents with OCD (Pediatric OCD Treatment Study [POTS] Team 2004), most guidelines recommend CBT as the first-line treatment for this population before any medication is started (Weidle *et al.* 2021).


EXRP
Individual/group ideally involving family/caregivers
Partial/no response
Trial of SSRI + ongoing EXRP
Partial/no response despite trial of SSRI for at least 12 weeks up to maximum recommended/tolerated dosage
1. Confirm adherence to medication and to EXRP and reconsider diagnosis and comorbidities.
2. Try an alternative SSRI and/or more intensive EXRP.
3. Try clomipramine (with appropriate medical screening and with toxicity and cardiac monitoring as necessary).
4. Seek expert consultation.

FDA-approved medications for pediatric OCD

Agent	Approved ages	Approved dosage
Sertraline	6–17	200 mg/day
Fluoxetine	7–17	Adolescents, higher-weight children: 60 mg/day Lower-weight children: 30 mg/day
Fluvoxamine	8–17	Ages 8–11: 200 mg/day Ages 12–17: 300 mg/day
Clomipramine	10–17	3 mg/kg or 200 mg/day, whichever is less

FIGURE 52-2. Treatment algorithm for OCD in children and adolescents.

EXRP = exposure and response/ritual prevention; SSRI = selective serotonin reuptake inhibitor.

In children and adolescents who experience an inadequate response to an initial CBT trial, SSRIs are considered second-line treatments. In the POTS trial, SSRIs had similar efficacy compared with CBT in 112 children and adolescents with OCD who were treated for 12 weeks. Notably, the combination of CBT and SSRIs was more effective than either treatment alone, and SSRIs were associated with a higher side-effect burden (POTS Team 2004). Of the SSRIs, only fluoxetine, fluvoxamine, and sertraline are FDA approved for the treatment of pediatric OCD in the United States, although there is little theoretical basis to suggest that these agents are superior to other available SSRIs. Clomipramine is also FDA approved for treating pediatric OCD, and it can be considered as a third-line agent in patients whose symptoms do not respond to two adequate SSRI trials (Varigonda *et al.* 2016).

Other pharmacological approaches studied in pediatric patients include augmenting SRIs with the glutamate modulators NAC and memantine (Ghanizadeh *et al.* 2017; Hezel *et al.* 2009; Li *et al.* 2020). Another glutamate modulator, D-cycloserine, has also been evaluated as a potential augmenter of CBT in children and adolescents with OCD (Wilhelm *et al.* 2018). Most other agents that have been tested in adults (including antipsychotics, stimulants, TMS, and neurosurgical approaches) have not been studied in pediatric populations and thus their use cannot be recommended. In particular, the use of antipsychotics should be avoided given the lack of support for their efficacy and their association with weight gain, metabolic syndrome, and other long-term adverse effects. Given the risk for adverse effects and limited information available to guide clinical decisions, seeking expert consultation is usually recommended when considering a trial of clomipramine or an experimental medication in children and adolescents with OCD.

Conclusion

OCD was once considered a rare and essentially untreatable condition. Although it remains a serious and debilitating disorder, fortunately our understanding of the phenomenology and treatment of OCD has improved dramatically over the past 40 years. Randomized controlled trials have established the efficacy of SRIs as first-line agents in OCD treatment. For those unresponsive to initial treatment, studies have also suggested next-step strategies, including switching to other serotonergic medications and augmenting with agents from other classes (e.g., antipsychotics, glutamate modulators). Preliminary studies have begun to identify and test new treatment approaches, including medications with novel mechanisms (e.g., ketamine, anti-inflammatories), pharmacological augmentation of CBT, and neuromodulation (e.g., TMS). Neurosurgical treatment remains available as a last resort. Some of the patients who receive the evidence-based treatments reviewed earlier (see Figures 52-1 and 5-2) can be expected to achieve wellness (i.e., minimal symptoms [Farris *et al.* 2013]), whereas even more will experience at least some symptom relief.

On the other hand, the substantial minority of patients who do not benefit from currently available treatments, or who cannot tolerate them due to side effects, is a reminder that we have much to learn. In particular, randomized controlled trials of medications with novel targets (i.e., those other than the monoamine systems) and of neuromodulation are needed to better establish the role of these approaches in OCD treatment. In addition, randomized controlled trials of medications in children and adolescents with OCD are sorely needed, given the limited research in pediatric populations to date. Other areas in need of further exploration include approaches to treating OCD comorbid with other psychiatric disorders, strategies to optimize the combination of psychopharmacology and psychotherapy for OCD, and ways to make the above treatments accessible to a broader and more diverse patient population.

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CHAPTER 53

Treatment of Schizophrenia

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Schizophrenia is a brain disorder characterized by a chronic relapsing and remitting course of psychosis that is often accompanied by persistent "deficit" features such as cognitive dysfunction and negative symptoms. This disorder seems to be similarly prevalent across geographical and cultural boundaries (Jablensky *et al.* 1992), affecting nearly 1% of the population (Charlson *et al.* 2018; Perala *et al.* 2007).

Considerable progress has been made in the pharmacological treatment of schizophrenia since the serendipitous discovery of chlorpromazine in the 1950s. Other antipsychotics, which share chlorpromazine's dopamine type 2 (D_2) receptor-blocking activity, were subsequently developed. These first-generation, or conventional, antipsychotics are all effective in the treatment of positive symptoms of psychosis but have limited beneficial effects on negative symptoms and cognitive deficits.

Since 1990, an array of second-generation agents have been developed. These medications have been referred to as atypical or novel antipsychotics because of their lower propensity (compared with many first-generation agents) to cause extrapyramidal side effects (EPS). This may contribute to the unique profile of some second-generation antipsychotics (Seeman 2002).

Pharmacological treatment should be personalized for each individual and include targeting positive symptoms of the illness as well as negative symptoms, cognitive impairment, and comorbid conditions while addressing potential side effects and physical health. Second-generation agents result in only modest improvement in mood, negative, and cognitive symptom clusters, which has led to hypotheses involving the effects of various receptor activities (e.g., serotonin type 7 [5-HT_7]) and to the development of compounds specifically targeted at negative and cognitive symptoms (Young and Geyer 2015). There has also been a concerted effort to develop antipsychotic medications with primary actions in the glutamatergic, muscarinic, trace amine-associated receptor 1 (TAAR-1), and D-amino acid oxidase systems.

In addition, schizophrenia has been increasingly conceptualized as a neurodevelopmental disorder (Insel 2010). In this context, the field has focused on early diagnosis and intervention during the prodromal phase, before the onset of overt psychosis, to improve the overall course or even prevent the onset of illness in individuals at risk of developing schizophrenia (Mei *et al.* 2021).

This chapter addresses the diagnosis and psychopharmacological treatment of schizophrenia as well as the common comorbidities of this illness.

Clinical Manifestations of Schizophrenia

There is a general consensus, following the seminal work of several investigators (Andreasen 1985; Crow 1985), that schizophrenia can be conceptualized as a disorder with at least two dimensions of symptomatology, in addition to the presence of cognitive impairments, that may be present at very different levels among individuals.

Positive Symptoms

Positive symptoms are perceptual or cognitive features that individuals without psychiatric disorders usually do not experience. They include hallucinations, delusions, and disorganized thinking, although disorganization also can be conceptualized as an independent symptom dimension (Liddle *et al.* 1989). Positive symptoms tend to respond to treatment with antipsychotic medications. These symptoms do not predict the long-term functional outcome of the illness (Green *et al.* 2000). Psychotic symptoms are not unique to schizophrenia; they can occur in a wide spectrum of other psychiatric, neurological, and medical disorders. Therefore, it is essential to rule out other possible causes of psychosis before a diagnosis of schizophrenia is made.

Negative Symptoms

Negative symptoms represent a "loss" of functions or abilities that people without schizophrenia usually possess. They include anhedonia, affective flattening, alogia, avolition, and asociality. Negative symptoms are associated with intellectual and neurocognitive impairment and are stronger predictors of long-term functional outcome than are positive symptoms (Harvey and Keefe 1998). However, neurocognitive deficits (discussed next) remain the strongest predictors of outcome (Green 1996).

The concept of primary versus secondary negative symptoms may provide a useful framework for assessing symptoms (Carpenter *et al.* 1988). *Primary* negative symptoms represent the core negative symptoms reflecting the disease process. *Secondary* negative symptoms, on the other hand, are caused by or are secondary to positive symptoms of psychosis or the antipsychotic medications themselves. A reduction in medication dosage may alleviate some secondary negative symptoms, but this strategy is unlikely to have a beneficial effect on primary negative symptoms.

Neurocognitive Deficits

People with schizophrenia also may experience a decline in cognitive functions, including verbal declarative memory, working memory, executive function, and attention. As described later in the section titled "Course of Schizophrenia," there is strong evidence that cognitive deficits predate the onset of psychosis in many people, followed by a significant decline during the early course of the illness (Keefe 2014; Lam *et al.* 2018). After this initial decline, cognitive function remains relatively stable without significant further deterioration (Heilbronner *et al.* 2016).

Diagnosis of Schizophrenia

According to DSM-5-TR (American Psychiatric Association 2022), to make the diagnosis of schizophrenia, there must be evidence of continuous symptomatic disturbance for at least 6 months accompanied by a decline from the premorbid level of functioning. This 6-month period can include functional deterioration occurring during the prodromal phase before the onset of overt psychosis. Within the 6-month period, the patient must have experienced two or more of the following symptoms for at least 1 month: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms; and one of these must be a positive symptom (delusions, hallucinations, or disorganized speech). If the duration of psychotic symptoms is less than 1 month because of successful treatment with antipsychotic medication, a diagnosis of schizophrenia may still be made.

Course of Schizophrenia

Schizophrenia may be characterized as a heterogeneous neurodevelopmental disorder in which psychotic symptoms develop in adolescence or young adulthood (McCutcheon *et al.* 2020). In the 2-5 years before the onset of the first psychotic episode, up to three-quarters of patients experience a range of nonspecific prodromal symptoms, demarcating an at-risk state for the development of psychosis or other mental disorders (Yung and McGorry 1996).

Clinically, the prodromal period is often characterized by depression, anxiety, social withdrawal, sleep disturbances, and reductions in motivation, cognition, and attention (Devoe *et al.* 2019). Transition from this prodromal period to the first psychotic episode is often triggered by an acute stressor that may include substance use (Devoe *et al.* 2019; Oliver *et al.* 2020). After the initial period of psychosis, the course is often characterized by a gradual deterioration in function over the next 5 years and then symptoms and functioning tend to stabilize, although some people experience full recovery from symptoms (Van Eck *et al.* 2018). The average age at onset is approximately 5 years later in women than in men, and women tend to have more favorable outcomes.

Schizophrenia is a highly heritable disease. Genome-wide association studies have found more than 200 genetic loci of interest associated with the risk of schizophrenia that contribute to the polygenic risk score for predicting likelihood of onset in a clinical population (Perkins *et al.* 2020; Ripke *et al.* 2014; Trubetskoy *et al.* 2022). Accumulating evidence (reviewed in Howes and Onwordi [2023] and McCutcheon *et al.* [2020]) indicates that genetic vulnerability and/or environmental stress lead to disruption in early brain development, potentially through alterations of synaptic expression, increasing the risk for schizophrenia. During adolescence, abnormal pruning may be driven by high *C4A* gene expression (Sekar *et al.* 2016). Decreased synaptic density or aberrant synapse function may then contribute to cortical excitatory-inhibitory imbalance and dysregulation in subcortical dopaminergic circuitry, leading to the development of cognitive and negative symptoms and positive symptoms of psychosis, respectively.

Functional outcomes are more closely associated with the level of cognition than with the severity of positive symptoms (Green 2016; Wells *et al.* 2015). Several large-scale studies have demonstrated that individuals with schizophrenia can be separated into three groups based on the trajectory of cognition as measured by IQ: the first group demonstrates early childhood cognitive impairment manifesting with low IQ and a global pattern of neurocognitive deficits; a second group demonstrates relatively stable cognitive development through adolescence and intact cognition despite emerging psychosis and intermittent positive symptoms over time; and a third group demonstrates steep decline in cognition during the adolescent period (Dickinson *et al.* 2020; Weinberg *et al.* 2016). Brain volume and genetic risk have been shown to cluster along these three trajectories (Dickinson *et al.* 2020; Weinberg *et al.* 2016). Individuals in the preadolescent cognitive impairment and adolescent decline groups experience poorer functional outcomes with global neurocognitive impairment. Some studies have found that impairment in schizophrenia is associated with particular cognitive domains, such as processing speed, attention, executive function, nonverbal memory, and working memory (Niarchou *et al.* 2013; Taylor *et al.* 2020).

Although schizophrenia is clearly a heterogeneous condition, studies suggest a better prognosis, at least in the initial course of illness, when treatments are provided early to minimize the duration of untreated psychosis (Kane *et al.* 2015; Van Eck *et al.* 2018; Robinson *et al.* 2022). Thus, a major goal in the treatment of schizophrenia is early recognition and timely treatment.

Pharmacological Management of Schizophrenia

Acute Psychosis

The acute phase of schizophrenia is characterized by psychotic symptoms that often lead to agitation and severe distress. Affective symptoms such as depression and mania also may be present. Patients who are unable to care for themselves or who show a risk of harming themselves or others may require hospitalization to stabilize their symptoms.

Antipsychotic medications are widely used and largely effective for the treatment of acute psychosis. Treatment of a patient with acute agitation and psychosis may require parenterally administered antipsychotic medication. Many physicians still use a high-potency first-generation antipsychotic (often haloperidol) in conjunction with a benzodiazepine (e.g., lorazepam) and/or an anticholinergic drug (e.g., benztropine) for acute symptom management. Intramuscular administration of a second-generation antipsychotic, such as olanzapine or ziprasidone, is also common. When olanzapine is used intramuscularly, benzodiazepines should be avoided because of an increased mortality risk associated with the combination (Marder *et al.* 2010).

If the patient has a history of treatment with antipsychotic medications, the clinician should ascertain whether the current psychosis is the result of nonadherence to the medication regimen, treatment resistance, or loss of therapeutic response to the medications. Patients often decide to stop taking antipsychotic medications, leading to symptom exacerbation or full-blown relapse (Mi *et al.* 2020). Reasons for stopping antipsychotics vary, but the most common are unpleasant side effects, anosognosia, delusional interpretations about medical care, substance use, and lack of a supportive environment (Kampman and Lehtinen 1999; Lacro *et al.* 2002). When patients choose to stop medication, it is imperative 1) to elicit and understand the reasons for their choice, 2) to provide psychoeducation to patients and their key supporters about risks of untreated psychosis, 3) to explore strategies to increase adherence or alternative treatment options, and 4) to develop a plan for medication and other treatment use going forward, which may include daily support and monitoring. Long-acting injectable medications should be considered, although long-acting medications do not guarantee long-term adherence (Kishimoto *et al.* 2018). In the case of treatment resistance or breakthrough psychosis while the patient is taking medication regularly, a change in the patient's medication regimen may be indicated.

Causes of psychosis exacerbation may include comorbid substance use disorder as well as trauma or other psychosocial stressors such as difficulties with housing, employment, benefits, insurance, disability, family members, or friends. Therefore, although medications are an important component in the treatment of psychosis, other interventions such as psychotherapy, group therapy, family therapy, dual-diagnosis treatment, social skills training (SST), and case management are important adjuncts to pharmacological management to improve coping at every stage of illness.

First-Episode Psychosis

Emphasis on the early diagnosis and treatment of the first psychotic episode of schizophrenia arises from evidence suggesting that longer durations of untreated psychosis may be associated with poorer long-term outcomes (Albert and Weibell 2019). Unfortunately, the average time between onset of symptoms and initiation of treatment in the United States has been up to a year and a half (Addington *et al.* 2015). Coordinated specialty care provided to patients and their families as early as possible in the course of illness reduces the duration of untreated psychosis, improves outcomes, and may reduce disability (Correll *et al.* 2018; Kane *et al.* 2016).

Because of their reduced risks of neurological side effects (parkinsonism, akathisia, and tardive dyskinesia), the second-generation antipsychotics are commonly used in the initial treatment of people in their first episode of psychosis. Because patients are likely to require long-term treatment, clinicians should choose medications with the lowest risk for cardiometabolic side effects (weight gain, hyperlipidemia, and glucose intolerance), monitor side effects regularly in accordance with published guidelines (American Diabetes Association *et al.* 2004), and adjust medication types and dosages based on their efficacy and tolerability. To provide the flexibility to switch from oral to long-acting injectable agents, clinicians may encourage initial use of medications that are available in both

formulations and effective in first-episode psychosis, including paliperidone, risperidone, aripiprazole, and olanzapine (Kane *et al.* 2020).

In discussing medication options with patients and their families, clinicians can use a shared decision-making approach (Deegan and Drake 2006) to maximize tolerability and ultimately adherence. Medications should be initiated at very low dosages, as these patients often respond robustly to low doses and are sensitive to side effects (American Psychiatric Association 2021). If needed, the dosage can be slowly titrated up to produce a full response.

After remission of an initial episode of psychosis, many patients are interested in tapering off medication. However, 10 randomized controlled trials demonstrated that relapse rates were twice as high among individuals who discontinued antipsychotic medication compared with those who maintained antipsychotic use during the first 24 months of treatment, and the risk was not different based on sudden versus gradual discontinuation; however, almost half of patients in the discontinuation groups did not experience relapse (Kishi *et al.* 2019). Predictors of relapse include antipsychotic nonadherence, persistent substance use disorder, criticism from caregivers, and poorer premorbid function (Alvarez-Jimenez *et al.* 2012). A careful, personalized discussion about medication risks and benefits should guide any decision to taper medication, and tapers should be conducted very slowly, with close monitoring during and afterward to allow for rapid reinitiation of medication if needed (Horowitz *et al.* 2021).

Choice of Antipsychotics

Since the early 1990s, second-generation antipsychotics have been used widely. Two government-sponsored studies, the U.K. National Health Service Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS; Jones *et al.* 2006), and the U.S. National Institute of Mental Health-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; Lieberman *et al.* 2005), demonstrated similar effectiveness between first-and second-generation antipsychotics. The CATIE study was designed to compare the effectiveness of four second-generation antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) and a representative first-generation antipsychotic (perphenazine) in "real-world" patients with schizophrenia. The primary outcome measure was treatment discontinuation. Of the 1,432 participants who received at least one dose of medication, 74% discontinued the study medication before 18 months: 64% of the subjects taking olanzapine discontinued compared with 74%-82% of those taking perphenazine, quetiapine, risperidone, or ziprasidone. More subjects receiving olanzapine discontinued because of weight gain and metabolic effects, whereas more subjects assigned to perphenazine discontinued because of EPS. For patients whose symptoms failed to improve with a newer second-generation antipsychotic, clozapine was more effective than switching to another second-generation antipsychotic (McEvoy *et al.* 2006).

Since the CATIE study was published, many new antipsychotics (e.g., asenapine, brexpiprazole, cariprazine, iloperidone, lurasidone, lumateperone, olanzapine-samidorphan, paliperidone) have been approved by the FDA. A very limited number of direct-comparison studies seem to suggest that these new antipsychotics are neither more nor less efficacious compared with older second-generation antipsychotics (Fu *et al.* 2014).

Neither the CATIE nor the CUtLASS study addressed the comparative effects of oral versus long-acting injectable antipsychotics. A meta-analysis of the many types of trials of long-acting injectable antipsychotics demonstrated a benefit for reducing relapse and rehospitalization (Kishimoto *et al.* 2021), as was demonstrated in a pragmatic

clinical trial among patients in their first episode (Kane *et al.* 2020). At present, risperidone, paliperidone, olanzapine, and aripiprazole are available in long-acting injectable formulations, and others are expected to be developed in the coming years.

Although antipsychotics can be highly effective for many people, they are not without their shortcomings. Patients need to be well informed about the different tolerability profiles among antipsychotic medications. As is discussed in more detail later in this chapter (see "Management of the Side Effects of Antipsychotic Medications"), several of the first-generation agents carry a high risk of EPS and tardive dyskinesia (Glazer 2000). Risperidone and paliperidone may elevate serum prolactin levels and may cause EPS at higher dosages. Iloperidone may elevate serum prolactin to a lesser degree. Akathisia and other EPS may be common with aripiprazole, brexpiprazole, cariprazine, and lurasidone. Weight gain and metabolic disturbances are associated with many antipsychotic medications, with olanzapine and clozapine having the highest likelihood and lurasidone the lowest likelihood of these effects (Bernardo *et al.* 2021). Sedation is most common in patients receiving asenapine, quetiapine, olanzapine, ziprasidone, or clozapine. Ziprasidone, paliperidone, and iloperidone may cause QTc interval prolongation and should be used with caution in patients at risk for this effect. Finally, because of its risks for agranulocytosis, seizures, and myocarditis, clozapine is generally reserved for patients with treatment-resistant illness or suicidality. However, experts recently recommended a tailored titration approach based on personal ancestry and monitoring to improve the safety of using this medication (de Leon *et al.* 2022). Table 53-1 lists the available formulations for the commonly used first-generation antipsychotic medications and all of the second-generation agents.

TABLE 53-1. Antipsychotic medications

Antipsychotic name	**Tablet/capsule**	**Orally disintegrating tablet**	**Liquid**	**Short-acting injection**	**Long-acting injection**	**Other**
Commonly used first-generation agents						
Chlorpromazine (low potency)	X		X	X		
Perphenazine (midpotency)	X					
Perphenazine-amitriptyline	X					
Loxapine (midpotency)	X					X[a]

[a] Loxapine inhalation powder.

[b] Asenapine transdermal patch.

[c] Risperidone long-acting injection includes intramuscular and subcutaneous formulations.

Antipsychotic name	**Tablet/capsule**	**Orally disintegrating tablet**	**Liquid**	**Short-acting injection**	**Long-acting injection**	**Other**
Fluphenazine (high potency)	X		X	X	X	
Haloperidol (high potency)	X		X	X	X	
Second-generation agents						
Aripiprazole	X	X	X		X	
Asenapine		X				X[b]
Brexpiprazole	X					
Cariprazine	X					
Clozapine	X	X	X			
Iloperidone	X					
Lumateperone	X					
Lurasidone	X					
Olanzapine	X	X		X	X	
Olanzapine-fluoxetine	X					
Olanzapine-samidorphan	X					
Paliperidone	X				X	
Quetiapine	X					
Risperidone	X	X	X		X[c]	
Ziprasidone	X			X		

[a] Loxapine inhalation powder.

[b] Asenapine transdermal patch.

[c] Risperidone long-acting injection includes intramuscular and subcutaneous formulations.

Maintenance Treatment

The major goals of maintenance treatment are to prevent relapse and to improve psychosocial and vocational functioning. Tailored psychopharmacological and psychosocial treatments should be combined to treat psychosis and improve functioning. The treatment and prevention of other psychiatric comorbidities is an important aspect of maintenance treatment. In addition, the prevention and treatment of medical comorbidities has become a very important part of long-term management.

Prevention of relapse improves long-term clinical outcomes. With each relapse, the time required to regain clinical stability typically lengthens, with the possible consequence of greater treatment resistance. Because nonadherence to medication is a significant predictor of relapse, clinicians must work with patients to develop a medication regimen that is acceptable to the patient. Ongoing use of shared decision-making (Deegan and Drake 2006) to find a medication regimen that is acceptable to the patient is key; this process can enhance communication, develop collaboration in working toward mutually agreed-upon goals, and identify areas of agreement that can lead to better overall medication tolerance and adherence and illness recovery (Hamann *et al.* 2020). Recently, experts recommended simplifying medication taking by using a single daily oral dose or a monthly or quarterly injection as well as improving tolerability by using lower doses (Takeuchi *et al.* 2021).

Treatment of Persistent Psychotic Symptoms

At least 30% of patients will have persistent psychotic symptoms despite consistent use of antipsychotics (Wagner *et al.* 2020). This treatment-refractory or treatment-resistant

psychosis is defined by 1) the lack of significant response to at least three adequate trials of antipsychotics from at least two different chemical classes in the past 5 years and 2) persistently poor social and occupational functioning.

Available data indicate that clozapine is the most effective drug for treatment-resistant schizophrenia (Siskind *et al.* 2016). Practice guidelines consistently recommend a trial of clozapine for patients who experience persistent psychotic symptoms. However, because of the serious side effects that may be associated with clozapine and the requirement for frequent white blood cell count monitoring in many countries, some patients and psychiatrists are reluctant to use this agent; thus, many patients with treatment-refractory psychosis never receive a trial. Among those who do, approximately a third experience persisting symptoms.

Multiple controlled trials have assessed whether combining two antipsychotics is more effective than antipsychotic monotherapy. Although augmentation with aripiprazole, fluoxetine, or valproate may provide benefit for individuals who experience minimal treatment response to clozapine (Siskind *et al.* 2018), the overall evidence for combining two antipsychotics is mixed and inconclusive. Many patients taking two antipsychotics can safely switch back to a single agent (Essock *et al.* 2011). Given the heterogeneity of treatment-refractory presentations, more research is needed to guide personalized treatment for patients with severe and resistant symptoms.

Treatment of Cognitive Deficits

Neurocognitive deficits, especially disturbances in executive functioning, memory, and attention (Green *et al.* 2000), are closely associated with the long-term functional outcome of patients with schizophrenia. Second-generation antipsychotics may improve some aspects of cognition in schizophrenia more effectively compared with haloperidol, as found in meta-analysis reports (e.g., Desamericq *et al.* 2014). The therapeutic effects of the newer antipsychotics are most notable in measures of verbal fluency and executive functioning, whereas improvement in memory may be more limited. However, data from the CATIE trial showed that at 18 months of treatment, perphenazine was more effective than any of the second-generation antipsychotics in improving all domains of neurocognitive deficits (Keefe *et al.* 2007). It is not clear, however, whether statistically significant improvements in neurocognition measured in the laboratory translate into improved functional outcomes in terms of employment, school performance, or social roles, for example (Green 2002). When added to standard treatment, cognitive remediation--a training approach designed to improve cognitive skills and function--improves cognition with small to medium effect sizes (Lejeune *et al.* 2021). Exercise also has been shown in 10 trials to improve cognition (Firth *et al.* 2017).

Behavioral and Psychosocial Management of Schizophrenia

Despite the proven efficacy of antipsychotics in the treatment of schizophrenia, most patients continue to experience some degree of residual positive symptoms, negative symptoms, and cognitive deficits, and many have difficulty attaining or regaining their desired level of social and occupational functioning. To date, several different

types of psychosocial interventions have been empirically shown to improve function and/or reduce rates of relapse and rehospitalization, and a variety of treatments may assist patients in acquiring social and vocational skills and possibly in managing residual psychotic symptoms (Mueser *et al.* 2013). We review key interventions next.

To address functional goals, treatment is optimally delivered by a multidisciplinary team that includes a medical professional who can prescribe medication, a psychotherapist, and clinicians skilled in psychosocial rehabilitation, including employment and housing specialists. Programs that use clinical case managers to directly assist patients in accessing services and to provide the psychosocial interventions in a community environment where skills can be practiced are ideal (Rapp and Goscha 2004). Specialized programs for people in first-episode psychosis are tailored to young people and their families to maximize engagement, rapid stabilization, and return to psychosocial functioning (e.g., Mueser *et al.* 2015).

A growing number of studies have shown that psychosocial treatments can be effective when delivered via technology (e.g., Baumel *et al.* 2016; Ben-Zeev *et al.* 2018; Brunette *et al.* 2016; Garety *et al.* 2021; Gottlieb *et al.* 2013; Rotondi *et al.* 2010), potentially increasing their reach while maintaining quality and lowering the cost of psychosocial treatment. Of importance, the interaction between pharmacological and psychosocial treatments seems to be more than additive, as each can enhance the effects of the other and affect complementary domains of outcome (Marder 2000).

Psychotherapy for Psychosis

More than 60 randomized controlled trials have demonstrated that cognitive-behavioral therapy (CBT) for psychosis is an effective addition to antipsychotic medication for the treatment of positive and negative symptoms of psychosis at both early and later stages of illness (Hardy *et al.* 2019; McDonagh *et al.* 2022), for psychosis that has not responded to medication treatment (Burns *et al.* 2014), and for people who have a high risk for but have not developed psychosis (Zheng *et al.* 2022). CBT for psychosis includes an in-depth assessment of the individual's experience of psychosis, training in coping skills, development of a shared formulation, identification and tracking of automatic thoughts, cognitive restructuring, and relapse prevention (Rathod *et al.* 2008).

Other models of psychotherapy for people with psychosis include individual resiliency training, an adaptation of CBT for psychosis for broader use (Mueser *et al.* 2015). Family therapy and multifamily groups have also demonstrated efficacy in reducing relapse risk (McDonagh *et al.* 2022).

Family and Team-Based Illness Management

It has long been noted that patients with highly critical or overinvolved family members (so-called high-expressed-emotion families) have a higher risk of relapse (Brown and Rutter 1966). Multiple studies have established the efficacy of family psychoeducational interventions (involving education and training in communication, problem-solving techniques, and/or cognitive and behavioral management strategies) in preventing relapse and improving other outcomes (McDonagh *et al.* 2022). The positive effect of family interventions persists beyond the time of the intervention (Sellwood *et al.* 2001) and is independent of both the specific form and the intensity of the intervention (Bustillo *et al.* 2001).

Assertive community treatment (ACT) has also demonstrated effectiveness in preventing relapse or rehospitalization for individuals with schizophrenia. ACT provides intensive multidisciplinary team management and service delivery in community settings for individuals who experience significant symptoms and high levels of functional impairment. At least 30 studies of ACT have shown advantages over standard treatment in reducing symptoms, family burden, and hospitalization rates and in improving independent living, housing stability, and quality of life (McDonagh *et al.* 2022; Phillips *et al.* 2001). However, it seems that the advantages of ACT do not persist after discontinuation of the program, even after prolonged delivery of services.

Interventions for Social and Vocational Functioning

SST is a strategy to help individuals acquire interpersonal disease management and independent living skills. A recent meta-analysis of 27 studies with comparators demonstrated that SST is an efficacious intervention for negative symptoms, general psychopathology, and social outcome measures when added to standard treatment including antipsychotic medication (Turner *et al.* 2018). Reviews of SST (Bellack and Mueser 1993; Kopelowicz *et al.* 2006) have described three models: basic, social problem-solving, and cognitive remediation.

Within the *basic model* of SST, complex social scenarios are broken down to simpler components, the therapist models behaviors, and the patient learns through repeated role-play. The *social problem-solving model* focuses on impaired information processing, which is thought to cause social skills deficits. This model targets symptom and medication management, recreation, basic conversation, and self-care in educational modules and is shown to be modestly effective in enhancing skills. Interventions that use cueing and support in everyday community interactions by friends or family members improve transfer of newly learned social skills to community functioning (e.g., Glynn *et al.* 2002). Finally, the *cognitive remediation model* of SST targets deficits in areas such as attention, memory, and planning, with the aim of supporting more complex cognitive processes used in learning social and other skills. An integrated approach to the concomitant training of neurocognitive and social cognitive abilities as well as social skills results in long-term improvement in social adjustment. One recent trial reported greater cognitive and functional gains when cognitive remediation was combined with physical exercise (Malchow *et al.* 2015).

Illness Management and Recovery (IMR) is a manualized package of empirically supported approaches (psychoeducation, cognitive-behavioral approaches for medication adherence, relapse prevention planning, SST, and coping skills training) delivered in weekly group or individual sessions that are used with a recovery focus that targets each individual's personal life goals (Mueser *et al.* 2006). This combination of approaches results in improved symptoms, better community functioning, and reduced hospital readmission (Bartholomew and Zechner 2014).

Although family psychoeducation, CBT, SST, and IMR may improve symptoms and social functioning, they do not seem to affect employment status. Supported employment programs have demonstrated efficacy in achieving substantial employment rates (Carmona *et al.* 2017) through rapid job searches, on-the-job training, continuous job support, and integration with mental health treatment, and they are more effective than traditional methods in helping patients obtain competitive employment. For young

people early in the course of their illness, this effective approach has been expanded to include return to education as well as employment (Ellison *et al.* 2015).

Independent housing is an important marker of community functioning. Simple provision of access to affordable housing by Section 8 certificates improves housing stability (Hurlburt *et al.* 1996). Supported housing, broadly defined as access to independent housing of the patient's choice (often supported with housing subsidies) coupled with access to community mental health and support services, improves residential stability and reduces hospitalization (Rog 2004). ACT for homeless individuals also has been shown to reduce homelessness (Coldwell and Bender 2007).

Patients and their families need information about psychosocial treatment options and should be engaged in discussions with their treatment providers about how these treatments can be useful in the context of an individual's symptoms, comorbidities, needs, and preferences.

Management of the Side Effects of Antipsychotic Medications

Pharmacological treatment of individuals with schizophrenia includes careful monitoring and management of the side effects of antipsychotics and other medications (Stroup and Gray 2018). Many patients may not spontaneously report side effects, particularly those that may be personal or embarrassing; therefore, treating clinicians can incorporate routine, systematic side-effect monitoring according to consensus guidelines into regular treatment visits (Table 53-2) (American Psychiatric Association 2021).

TABLE 53-2. Schedule for monitoring antipsychotic medication side effects

	Baseline	4 Months	Quarterly	Yearly
Metabolic				
Serum electrolytes, renal function tests, complete blood count with differential, and liver function tests	X			
Weight and height for BMI[a]	X		X	
Fasting serum lipid panel and glucose or hemoglobin A1C[b]	X	X		X

	Baseline	4 Months	Quarterly	Yearly
Hyperprolactinemia symptoms and serum prolactin[c]	X			X
Neurological				
Examination for extrapyramidal side effects, including tardive dyskinesia[d]	X			X
Cardiovascular				
Electrocardiogram to assess for QTc > 450 ms[e]	X			
Blood pressure, heart rate[f]	X			

[a] Calculated as weight in kilograms divided by height in meters squared. Take before medication initiation and monthly for first 6 months after medication initiation, then quarterly thereafter.

[b] Take before medication initiation, at 3-4 months after medication initiation, and then at least yearly thereafter.

[c] Symptoms of hyperprolactinemia should be assessed at each visit until dosing is stable, and then yearly; check serum prolactin when symptoms are present.

[d] Assess at every visit. Assess and document with assessment tools (e.g., Abnormal Involuntary Movement Scale) at least yearly, and every 6 months for high-risk patients (women, individuals older than 55 years, and those with neurological injury, past extrapyramidal side effects, and use of high dopamine$_2$-blocking antipsychotics).

[e] To assess for QTc interval prolongation before and after initiation and dosage increase in high-risk patients and with the use of chlorpromazine, droperidol, iloperidone, pimozide, sertindole, thioridazine, or ziprasidone.

[f] Taken at the initial visit and then as medically indicated.

Adverse Metabolic Side Effects and Obesity

Medication side effects, as well as lifestyle and intrinsic factors associated with schizophrenia, place patients with this disorder at increased risk for weight gain and the development of dyslipidemia, glucose intolerance, type 2 diabetes, and diabetic ketoacidosis (Freyberg *et al.* 2017). This metabolic dysregulation contributes to the development of cardiovascular diseases and the shortened life span associated with schizophrenia (Correll *et al.* 2017).

A substantial proportion of patients receiving an antipsychotic medication experience clinically significant weight gain, although weight gain propensity varies among antipsychotic medications (Pillinger *et al.* 2020). For example, the CATIE investigators found a greater than 7% weight gain from baseline in 30% of individuals receiving olanzapine, 14% of those receiving risperidone, and 7% of those receiving ziprasidone (Lieberman *et al.* 2005). This weight gain is often located in the abdomen, the region most implicated in insulin resistance (Sarsenbayeva *et al.* 2019). Weight gain and other cardiometabolic side effects may be substantially greater in young people using an antipsychotic for the first time (Tek *et al.* 2016), and obesity is already associated with hypertension in these young people (Brunette *et al.* 2023).

Insulin resistance and diabetes occur two to four times more frequently in patients with schizophrenia compared with the general population (Dixon *et al.* 2000) and may occur during antipsychotic treatment in the absence of weight gain (Ballon *et al.* 2014). The risk of diabetes is likely multifactorial, but evidence clearly indicates that antipsychotics are associated with glucose dysregulation (Jin *et al.* 2004), with clozapine and olanzapine associated with the greatest risk (Pillinger *et al.* 2020). Two genes associated with schizophrenia, Akt serine/threonine kinase (*AKT1*) and neuregulin 1 (*NRG1*), may play a role in systemic metabolic regulation (Freyberg *et al.* 2017).

Hyperlipidemia is also associated with the use of many second-generation antipsychotics (particularly clozapine, olanzapine, and quetiapine) as well as low-potency first-generation medications (Buhagiar and Jabbar 2019). The co-occurrence of atherogenic dyslipidemia with abdominal adiposity, insulin resistance, impaired fasting glucose or overt diabetes mellitus, and hypertension--known as metabolic syndrome--is associated with a significantly elevated risk for cardiovascular disease. More than 40% of CATIE participants demonstrated metabolic syndrome at baseline, with women carrying greater risk than men (McEvoy *et al.* 2005). Metabolic syndrome is associated with lower levels of aerobic fitness and greater functional impairment (Vancampfort *et al.* 2015).

The metabolic status of patients with schizophrenia should be monitored before and after treatment initiation (American Diabetes Association *et al.* 2004). Lipids, fasting glucose, and/or hemoglobin A1C should be checked at baseline, after 4 months of treatment, and annually thereafter or more frequently if dysregulation is detected. Weight to calculate BMI and blood pressure should also be checked frequently. Patients should be coached on diet and exercise strategies for metabolic health, with iterative goal-setting, progress monitoring, and discussion of impact on mental and physical health (Noordsy and Yudofsky 2019). Mental health providers should ensure that patients access primary care and should coordinate with primary care providers, particularly when metabolic symptoms become more concerning. When cardiometabolic side effects are detected, treatment providers should rapidly address the problems by switching medications or providing other behavioral or pharmacology strategies. Cardiometabolic health and side-effect risks should be a part of shared decision-making for antipsychotic treatment with patients because, for many, weight gain leads to medication discontinuation or underuse; thus, management of weight and cardiometabolic side effects has strong implications for overall adherence and clinical outcome (Vancampfort *et al.* 2019).

To avoid adverse metabolic side effects and obesity, prescribers should initiate treatment with or switch patients to antipsychotics that carry a lower risk for cardiometabolic side effects, such as a partial dopamine agonist (aripiprazole, brexpiprazole, or cariprazine) or another lower-risk second-generation antipsychotic (e.g., lurasidone, lumateperone, ziprasidone). If a patient's symptoms do not respond optimally, progression to a higher-risk antipsychotic with strong efficacy data (olanzapine or clozapine) may prove necessary. Olanzapine-samidorphan includes an opiate antagonist with potent m opioid receptor inhibition (Chaudhary *et al.* 2019) that reduces weight gain associated with olanzapine (Martin *et al.* 2019). There is no evidence yet of benefit for other metabolic parameters (Correll *et al.* 2020). Other drug targets under development for mitigating the metabolic side effects of antipsychotics include glucagon-like peptide 1 agonists, TAAR-1 agonists, and glucocorticoid/mineralocorticoid receptor antagonists.

Several other medications can be considered for off-label use to manage antipsychotic-induced metabolic dysfunction. Metformin prevents weight gain at the initiation of antipsychotic therapy and also induces modest weight loss relative to placebo (3 kg with metformin vs 1 kg with placebo) during continuation therapy (Jarskog *et al.* 2013). Moreover, metformin in combination with lifestyle changes has been found to be effective in decreasing other cardiometabolic risks (Zheng *et al.* 2019). Topiramate has also shown promise as a weight-reducing agent, although cognitive side effects may limit its utility, and it is unclear whether it is effective when used with clozapine (Correll *et al.* 2016). Glucagon-like peptide 1 receptor agonists (e.g., semaglutide) are increasingly used for weight loss (Siskind *et al.* 2019). In extreme cases, bariatric surgery may also be considered and has shown good effects on weight loss. Centrally acting sympathomimetic weight-loss drugs have the potential to increase the activity of biogenic amines and may exacerbate symptoms of psychosis in this population (Jo *et al.* 2019); thus, they should be used with extreme caution.

Neurological Side Effects

Dystonia, parkinsonism, and akathisia--known as EPS--are common neurological adverse conditions caused by antipsychotic medications. EPS are thought to arise from extensive antagonism of dopamine receptors in the striatum (Howes and Kapur 2009). Medications that block postsynaptic dopamine activity result in increased muscarinic cholinergic activity in this circuit, precipitating EPS progression (Snyder *et al.* 1974). Risk varies by antipsychotic, with the highest risk associated with antipsychotics that provide potent D_2 receptor blockade (Leucht *et al.* 2013; Shirzadi and Ghaemi 2006).

Dystonia involves spontaneous, uncontrollable muscle contractions that can be painful and distressing. These contractions may present as cervical dystonias (retrocollis and torticollis), blepharospasm, trismus, tongue protrusion, oculogyric crisis, and laryngospasm. Severe laryngospasm, with dysphagia, aspiration, and choking, can be life-threatening and thus requires immediate treatment (Kulkarni *et al.* 2017). Dystonia occurs most commonly in young male individuals shortly after the initiation of a new antipsychotic medication or following an abrupt or rapid dosage increase, with most cases occurring within 5 days of starting a medication. Approximately 5% of patients treated with intramuscular haloperidol for agitation experience dystonia within 24 hours, compared with fewer than 1% of those treated with a second-generation antipsychotic (Satterthwaite *et al.* 2008).

Antipsychotic-induced parkinsonism includes symptoms of muscle rigidity, resting tremor, bradykinesia, and affective flattening (i.e., masked faces) that occur gradually over days to months and that are more common among women and older individuals (Thanvi and Treadwell 2009). Parkinsonism is thought to result from D_2 receptor antagonism in the nigrostriatal dopamine circuit. Medication-induced parkinsonism can also precipitate anhedonia and apathy, which may be differentiated from depression and negative symptoms of schizophrenia by the presence of motor symptoms. Rabbit syndrome is a variant of parkinsonism that is characterized by a perioral and jaw tremor (Casey 1999).

Akathisia is an acute feeling of uncontrollable restlessness or an inability to remain seated or sit still. The mechanism of antipsychotic-induced akathisia is not well understood but is thought to arise from abnormal activity of the striatum affecting the adrenergic system. Medications that have lower D_2 receptor-blocking activity, partial D_2 agonist activity, or greater anticholinergic properties may be less likely to cause akathisia and are better tolerated by those who develop this side effect (Leucht *et al.* 2013; Satterthwaite *et al.* 2008).

Clinicians should regularly monitor patients for EPS using structured ratings before and after medication initiation and dosage increases (Barnes *et al.* 2020; Stroup and Gray 2018). Treatments that address EPS reduce the muscarinic cholinergic activation resulting from dopamine blockade or facilitate dopamine release. Providers can treat dystonias with anticholinergic or antihistaminergic medications such as benztropine, trihexyphenidyl, or diphenhydramine. Intramuscular anticholinergics should be used to treat acute and severe dystonias that require rapid resolution. Preventive treatment may be used for high-risk patients who require a medication with potent D_2 blockade (Satterthwaite *et al.* 2008). Dosage reduction of the antipsychotic medication should be considered first for the treatment of parkinsonism and akathisia, although resolution of these side effects may take months. Akathisia may be addressed acutely through antagonism of b-adrenergic receptors (propranolol, clonidine) or the serotonin type 2A receptor (mirtazapine) (Poyurovsky *et al.* 2006); anticholinergic and benzodiazepine agents offer limited benefit. Although benzodiazepines may reduce akathisia, their habit-forming potential should limit their use.

Tardive Dyskinesia and Tardive Dystonia

Tardive dyskinesia, a syndrome of potentially irreversible involuntary choreiform movements, and tardive dystonia, characterized by sustained muscle contractions, can gradually emerge after months of treatment with antipsychotic medications that block dopamine receptors. Because the risk of tardive dyskinesia is cumulative, it may emerge after years of treatment. These side effects typically persist beyond 1 month after medication discontinuation and can be disfiguring and debilitating (Savitt and Jankovic 2018). First-generation antipsychotic medications carry a higher long-term risk for tardive syndromes compared with second-generation medications, with rates of 32% and 13% (Correll and Schenk 2008), or 6.5% versus 2.6% per year (Carbon *et al.* 2018), respectively. Among the second-generation antipsychotics, risperidone and paliperidone confer the highest risk. Tardive dyskinesia is most common among older women, whereas tardive dystonia is more common in younger men (Solmi *et al.* 2018a). The risk for tardive dyskinesia is a robust reason for choosing second-over first-generation agents.

Tardive dyskinesia involves abnormal movements of the orofacial and buccolingual musculature manifesting as grimacing, lip smacking, chewing, and rhythmic movements of the tongue. Involvement of the neck, axial, and extremity musculature may also occur in the form of choreoathetoid movements, which may involve the laryngopharyngeal and respiratory muscles. Tardive dystonia may appear earlier in treatment than tardive dyskinesia and is characterized by slow, sustained twisting movements of the head, neck, trunk, and extremities, as well as blepharospasm, torticollis, back arching, and hyperextension of the limbs. Withdrawal tardive dyskinesia is a form of the disorder that may occur upon dosage reduction or discontinuation of an antipsychotic.

Patients who are taking antipsychotic medications should be regularly screened for tardive dyskinesia and tardive dystonia with structured rating instruments. These side effects can be addressed by reducing the dosage of the antipsychotic medication or switching from first-to second-generation agents with the lowest risk for this side effect (e.g., clozapine, olanzapine, or quetiapine) (Margolius and Fernandez 2019). Anticholinergic medications should be discontinued, as they can worsen these symptoms. For individuals with moderate to severe tardive dyskinesia, vesicular monoamine transporter 2 (VMAT2) inhibitors (e.g., deutetrabenazine, valbenazine) may be used (Solmi *et al.* 2018b). Deep brain stimulation can be considered for severe, refractory tardive syndromes. Botulinum toxin injections may be used for localized severe, refractory tardive dystonia.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening condition that can arise from the use of antipsychotics. The incidence of NMS was previously as high as 3%; however, more conservative prescribing practices and monitoring have likely reduced the incidence to as low as 0.01%-0.02% (Strawn *et al.* 2007). Using a nationally representative Finnish database (1972-2017), researchers reported that the rate of NMS was 0.0002% per person-year, with a death rate of 4.7% in the first month after diagnosis (Guinart *et al.* 2021). Risk factors include rapidly escalated and high dosages of antipsychotics; concomitant use of anticholinergics, lithium, and benzodiazepines; and

cardiovascular disease, catatonia, dehydration, and use of restraints (Berardi *et al.* 2002; Guinart *et al.* 2021). Symptoms of NMS include hyperpyrexia, altered consciousness, muscle rigidity, dystonia, and autonomic nervous system dysfunction. Laboratory studies may show elevated creatine phosphokinase, liver enzyme, and lactic acid levels and white blood cell counts (Strawn *et al.* 2007). Immediate treatment is crucial and includes discontinuation of antipsychotics, support of vital functions, intravenous access and fluid replenishment, and use of dopamine-potentiating agents (e.g., amantadine and bromocriptine) or muscle relaxants (e.g., dantrolene) (Pileggi and Cook 2016; Strawn *et al.* 2007). In treatment-refractory NMS, electroconvulsive therapy can be administered (Trollor and Sachdev 1999). Patients should remain off antipsychotic medications for 2 weeks after resolution of NMS before reinitiating antipsychotic treatment, which should begin with a trial of a low-dosage, low-potency antipsychotic (e.g., quetiapine or clozapine).

Hyperprolactinemia

D_2 receptor antagonism caused by first-and second-generation antipsychotics is thought to enhance the release of prolactin from the pituitary gland, leading to the signs and symptoms of antipsychotic-induced hyperprolactinemia. Medications with potent D_2 receptor-blocking effects, including most first-generation antipsychotics and some of the second-generation agents (e.g., risperidone, paliperidone, sertindole, and lurasidone) are associated with hyperprolactinemia, whereas medications with lower affinity for D_2 receptors or those that act as partial D_2 agonists (e.g., aripiprazole, brexpiprazole, cariprazine, quetiapine, and asenapine) are least likely to cause prolactinoma (Leucht *et al.* 2013). Chronically elevated serum prolactin levels can result in galactorrhea, gynecomastia, and sexual dysfunction in men as well as galactorrhea and abnormal menses in women (Haddad and Wieck 2004). Elevated serum prolactin has been associated with lower bone density in longitudinal studies (e.g., Wang *et al.* 2014), but not all studies show an association between prolactin and bone density (Lally *et al.* 2019).

Clinicians should ask patients about symptoms of hyperprolactinemia, including sexual side effects, which are concerning to patients and can lead to medication nonadherence. Serum prolactin levels should be obtained before initiating an antipsychotic, 3 months after treatment initiation, and annually thereafter (Grigg *et al.* 2017). Patients who develop hyperprolactinemia may benefit from switching to a medication with a lower propensity to cause this side effect.

Corrected QT Interval Prolongation

Several antipsychotic medications (e.g., chlorpromazine, droperidol, iloperidone, pimozide, sertindole, thioridazine, and ziprasidone) can delay cardiac ventricular repolarization, which increases the risk for torsades de pointes, an arrhythmia that can cause sudden cardiac death (Li and Ramos 2017). For individuals with cardiovascular risk factors, clinicians can assess their clinical history of palpitations, syncope, and dizziness as well as ordering an electrocardiogram to monitor for heart rate-corrected QT intervals before and after initiation of these medications. Other risk factors can be described as nonmodifiable (e.g., congenital long QT syndrome, age, sex, family history of sudden cardiac death, personal or family history of structural or functional heart disease, personal history of drug-induced QT prolongation, or metabolizer status)

and modifiable (e.g., starvation, bradycardia, excess dose or rapid intravenous infusion of QTc interval-prolonging drugs, simultaneous use of multiple drugs that prolong QTc intervals, or the risk or presence of hypokalemia, hypomagnesemia, or hypocalcemia or factors affecting drug metabolism such as drug-drug interactions, acute or chronic kidney disease, or hepatic impairment). If the QTc is greater than 450 ms or other risk factors are present, antipsychotic medications that do not cause this adverse effect should be used.

Management of Common Comorbidities in Schizophrenia

Tobacco Use Disorder

The rate of smoking among people with schizophrenia continues to be three times that seen in the general population (McClave *et al.* 2010). Cigarette smoking causes cardiovascular disease, diabetes, lung disease, and cancer and is partially responsible for excess disease burden and early mortality in schizophrenia (Callaghan *et al.* 2014). In contrast with the self-medication hypothesis, smoking abstinence does not worsen cognition or symptoms (Boggs *et al.* 2018; Evins *et al.* 2005), and quitting decreases the 10-year risk of morbidity and mortality without worsening psychosis (Thorndike *et al.* 2016).

Smoking can also complicate the treatment of schizophrenia. The hydrocarbons in smoke induce cytochrome P450 1A2 enzymes, lowering blood concentrations of clozapine and olanzapine (Tsuda *et al.* 2014). Smoke-free inpatient treatment settings reduce harm from secondhand smoke and provide a safe experience of being smoke-free (Robson *et al.* 2017). Clinicians may need to adjust antipsychotic dosages and provide nicotine replacement therapy (NRT) to treat withdrawal symptoms as patients transition in and out of smoke-free hospital settings or upon smoking cessation.

Effective intervention for cessation requires a multimodal approach that integrates motivation-based treatment (Brunette *et al.* 2020; Steinberg *et al.* 2016), behavioral addiction treatment strategies, and pharmacological treatment to address withdrawal and craving (Evins *et al.* 2019), ideally integrated into mental health treatment and provided when the patient is psychiatrically stable. Use of pharmacotherapy is safe and doubles or triples success rates (Evins *et al.* 2019). As in the general population, varenicline seems to be the most effective, followed by bupropion plus NRT, dual NRT (daily patch plus gum or lozenges as needed up to 20 times daily), or, with lower rates of effectiveness, bupropion or NRT monotherapy. Although relapse is a consideration for all smokers, those with schizophrenia experience relapse faster with discontinuation of pharmacotherapy; hence, maintenance pharmacotherapeutic and behavioral treatment for a year is important for this population (Evins *et al.* 2014). With treatment, patients with schizophrenia are able to quit smoking and thereby improve their long-term health without adverse effects on the psychotic illness.

Substance-Related Disorders

Nearly one-half of patients with schizophrenia have a lifetime history of an alcohol or drug (substance) use disorder, compared with 16% of the general population (Hunt *et al.* 2018; Regier *et al.* 1990). As in the general population, men with schizophrenia are more likely to abuse substances than are women, and the most commonly abused substances include alcohol, cannabis, opioids, and stimulants.

Without treatment, comorbid substance use disorders have a deleterious effect on the course of schizophrenia, including earlier onset of illness, worse symptoms, relapses, and hospitalizations (Grech *et al.* 1999; Schoeler *et al.* 2016) as well as early mortality (Heiberg *et al.* 2018). Among people who have not yet developed schizophrenia, psychotic syndromes triggered by substance use typically resolve within days or weeks after intoxication has resolved; however, in about a third of individuals, these syndromes may persist and develop into schizophrenia, most often with cannabis, hallucinogen, and amphetamine use (Murrie *et al.* 2020). There has been great interest in cannabis, the most frequently used illicit substance in schizophrenia (Murray *et al.* 2017). Its main psychoactive component, D-9-tetrahydrocannabinol, causes psychosis in a dose-dependent manner among patients without a cannabis use disorder, whereas cannabidiol does not (Ahmed *et al.* 2021). In some studies, approximately half of patients with first-episode psychosis already have a substance use disorder (Brunette *et al.* 2018), which complicates the diagnosis of the psychotic disorder.

Although obtaining information from patients about their use of substances should be a standard part of the medical history, problematic alcohol or substance use is often underrecognized and hence undertreated in psychiatric settings (Drake *et al.* 1993). Use of brief screening tools for substance use (e.g., Searles *et al.* 1990) can increase detection. In addition, patients often deny use; hence, clinicians should pursue collateral reports from family members, case managers, and others involved in the patient's care. Patients with schizophrenia and a comorbid substance use disorder require treatment for both disorders, optimally in programs that provide long-term comprehensive services along with integrated mental health and substance abuse treatment (Ziedonis *et al.* 2005), including motivational and cognitive-behavioral interventions, contingency management (Destoop *et al.* 2021), and medication management (Bennett *et al.* 2017).

Antipsychotic treatment should be utilized to stabilize the psychotic disorder and may reduce the use of substances as well. Regarding the choice of antipsychotic, a meta-analysis of 19 randomized controlled trials found some evidence of superiority for clozapine in the reduction of substance use, whereas risperidone and olanzapine reduced craving (Krause *et al.* 2019). Pharmacological treatment of alcohol and substance use disorders should also be utilized. The following approaches have been studied in schizophrenia: 1) disulfiram for co-occurring alcohol use disorder (note that use requires monitoring in patients with schizophrenia); 2) naltrexone for co-occurring alcohol use disorder; 3) the tricyclic antidepressants desipramine and imipramine for comorbid cocaine use disorder; 4) buprenorphine or methadone for opioid use disorder; and 5) NRT, bupropion, and varenicline for tobacco use disorder (for reviews, see Akerman *et al.* 2014 and Pratt *et al.* 2020; for opioid use disorder, see Lamont *et al.* 2020).

Depression

Schizophrenia is often associated with depressive states ranging from dysphoria to major depressive disorder (Blum *et al.* 2015; Siris 2000; Upthegrove *et al.* 2017). A meta-analysis of cross-sectional studies demonstrated that 35.5% of inpatients and 25.8% of outpatients had current depression, as assessed with the Calgary Depression

Scale for Schizophrenia (Li *et al.* 2020), whereas the lifetime prevalence of depression in schizophrenia is as high as 50%. Depression in schizophrenia is a risk factor for suicide and an indicator of poorer outcomes (Hawton *et al.* 2005).

Major depressive disorder in individuals with schizophrenia must be carefully differentiated from classic negative symptoms such as alogia and blunted affect, antipsychotic medication-induced dysphoria occurring with potent D_2 receptor blockade, parkinsonian EPS, and demoralization that may occur when patients struggle with illness-related symptoms and disability. Shared features of negative symptoms and depression may include anhedonia, avolition, social ambivalence, and anergia (Krynicki *et al.* 2018; McGlashan and Carpenter 1976). Use of the Calgary Depression Scale for Schizophrenia helps to establish a diagnosis of major depressive disorder, as it focuses on symptoms specific to the disorder, including worthlessness, hopelessness, feelings of guilt, and suicidal thinking (Addington *et al.* 1996).

Treatment of major depressive disorder in patients with schizophrenia may include both psychopharmacological and psychosocial interventions (Ceskova 2020; Hasan *et al.* 2015). Because depression symptoms may presage an increase in psychosis and also may occur with psychosis in schizophrenia, pharmacological treatment with antipsychotic medication should be optimized first. Most of the second-generation antipsychotics are more effective than placebo for reducing depression symptoms, whereas first-generation agents are not (Huhn *et al.* 2019). Consequently, in those treated with a first-generation antipsychotic, the dosage may be reduced or the medication changed to a second-generation antipsychotic. However, an episode of major depressive disorder that develops after the remission of psychosis may require the addition of an antidepressant. A meta-analysis demonstrated antidepressant effects for trazodone, duloxetine, sertraline, and amitriptyline (Helfer *et al.* 2016). In addition, SSRIs as a group were effective (seven trials, with 422 participants; standardized mean difference = -0.48 [95% CI: -0.84 to -0.11]; $P = 0.01$).

Other approaches may also be helpful. Early evidence suggests a possible role for the use of adjunctive omega-3 polyunsaturated fatty acids (Pawelczyk *et al.* 2016; Robinson *et al.* 2019). Psychosocial interventions such as CBT (Jones *et al.* 2012) and physical exercise (Dauwan *et al.* 2016) can improve depression and well-being. Severe depression may be treated with repetitive transcranial magnetic stimulation or electroconvulsive therapy, both effective treatments for unipolar depression with some evidence of benefit in the treatment of severe depression in those with schizophrenia (Ali *et al.* 2019; Ceskova 2020).

Suicide

Suicide is a major contributor to decreased life expectancy in people with schizophrenia, who have approximately a 5% lifetime risk of completed suicide (Hor and Taylor 2010; Palmer *et al.* 2005). The risk of suicide is highest among young adults in the early stages of the illness and continues over the life span (Olfson *et al.* 2021). Among hospitalized patients, the risk of suicide peaks immediately upon admission and shortly after discharge. Nearly 50% of people with schizophrenia attempt suicide during their lifetime.

The strongest risk factors for suicide include a previous history of suicide attempts, ideation, and history of self-harm as well as symptoms of depression and hopelessness, positive symptoms of psychosis, anxiety and insomnia, and alcohol or drug abuse in schizophrenia at any age (Hor and Taylor 2010; Popovic *et al.* 2014) and in first-episode psychosis (Bornheimer *et al.* 2021; Iyer *et al.* 2021). In contrast with general population risk factors, being intelligent with good premorbid functioning, high insight, and high personal hopes and expectations are risk factors for suicide in schizophrenia (Bornheimer *et al.* 2021; Fazel *et al.* 2014). Population-level studies have demonstrated that absence of medication treatment is associated with a higher rate of suicide compared with treatment with antipsychotic medication (adjusted relative risk = 37.4 [95% CI, 5.1 to 276]) (Tiihonen *et al.* 2006).

In mitigating suicide risk, the treating clinician should regularly assess for suicide risk and protective factors (Popovic *et al.* 2014). Antipsychotic therapy plays a crucial role in the prevention of suicide by treating psychosis and depression symptoms. Several studies have demonstrated the efficacy of clozapine over other drugs for managing suicidality in patients with schizophrenia (Meltzer *et al.* 2003; Taipale *et al.* 2021). Other second-generation antipsychotics may also have antisuicide effects, although the evidence is not as robust (Barak *et al.* 2004). For patients with concurrent depression, antidepressants added to antipsychotics decrease depression (Helfer *et al.* 2016) and risk of suicide (Haukka *et al.* 2008).

Electroconvulsive therapy may be helpful for high-risk patients (Pompili *et al.* 2013).

Patients who present with suicidal thoughts or behavior may require hospital care at times of high symptom acuity and close follow-up with intensive outreach and family involvement after discharge. Ward safety measures, substance use disorder and mood disorder treatment, and interventions to improve medication adherence address suicide risk factors. Psychosocial interventions for schizophrenia that directly address suicide (e.g., CBT) have been shown to reduce suicidal thoughts and behaviors in these patients (Bornheimer *et al.* 2020).

Obsessive-Compulsive Symptoms

Obsessive-compulsive symptoms (OCSs) occur in 10%-64% of patients with schizophrenia (Wehbe *et al.* 2019). Several national cohort studies demonstrate that individuals with OCSs or OCD are at a substantially elevated risk for the development of a psychotic spectrum disorder and vice versa (e.g., Meier *et al.* 2014), consistent with the substantial overlap in risk genes for the two disorders (Lee *et al.* 2019). OCSs or OCD can occur before, during, or after onset of psychosis as well as in the context of antipsychotic use, particularly clozapine (Sharma and Reddy 2019). Some neurocognitive deficits are common to both disorders, including difficulties with attentional set-shifting and executive functioning (Sahoo *et al.* 2018; Schirmbeck *et al.* 2013). Although OCSs may be difficult to distinguish from delusions, they are important to identify because they may indicate greater impairment that may be responsive to tailored treatment approaches (Faragian *et al.* 2012; Wehbe *et al.* 2019). Therapies used for OCD can be helpful in treating OCSs in individuals with schizophrenia, including serotonergic agents and CBT (Sharma and Reddy 2019).

Conclusion and Future Directions

Although antidopaminergic medications continue to play a major role in the treatment of the positive symptoms of schizophrenia, other mechanisms of action continue to be explored in addition to novel approaches for negative and neurocognitive symptoms. Recent drug development efforts include serotonin type 2A receptor antagonists, muscarinic agonists, TAAR-1 agonists, and D-amino acid oxidase inhibitors. Early clinical trials of muscarinic agonists have demonstrated some efficacy for psychosis, with an apparent lack of metabolic or neurological adverse events but substantial gastrointestinal side effects (Brannan *et al.* 2021). TAAR-1 agonists may be efficacious for negative symptoms, with predominantly somnolence and gastrointestinal adverse events (Koblan *et al.* 2020). If approved, agents with novel mechanisms and advantageous side-effect profiles could improve the balance of benefits over risks, potentially improving treatment adherence and overall outcomes for patients with schizophrenia.

In addition to recent pharmacological advances, other novel approaches are being explored. Real-time functional MRI neurofeedback has resulted in improved symptoms and amelioration of neural network abnormalities in the brain (Bauer *et al.* 2020; Humpston *et al.* 2020; Okano *et al.* 2020). Novel psychosocial approaches, including computerized cognitive remediation, may be of benefit in treating cognitive impairment in schizophrenia (Bowie *et al.* 2020). Mobile health interventions to improve illness management are showing promise (Buck *et al.* 2021; Chivilgina *et al.* 2020). Such interventions could improve treatment access and lead to better outcomes.

Further progress is expected in the development of treatments for prodromal schizophrenia, with the goal of improving symptoms and delaying or preventing conversion to the full expression of the illness. As new treatments for the negative and cognitive systems of schizophrenia emerge, these therapeutics may also have a role in the treatment of prodromal symptoms and perhaps the prevention of schizophrenia.

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CHAPTER 54

Treatment of Substance Use Disorders

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Substance use disorders are common in the United States. In 2019, approximately 57.2 million people (or 21% of the U.S. population) age 12 years or older reported past-year illicit drug use, with 8.3 million (3%) reporting at least one illicit drug use disorder and approximately 27 million reporting daily cigarette use (Substance Abuse and Mental Health Services Administration 2020). Therefore, many Americans are directly affected by substance use disorders, and millions more are affected through family or friends or through the societal costs associated with these disorders. The cost to society is astronomical, with annual hospital costs alone from emergency department visits and inpatient hospitalizations exceeding $13 billion in 2017 (Peterson *et al.* 2021). In 2017, the overall economic burden of opioid use disorders and opioid overdose deaths was estimated to be as high as $1.01 trillion, in large measure due to the value of life lost, lost health-related quality of life, lost productivity, and costs related to health care, treatment, and criminal justice (Florence *et al.* 2021).

Fortunately, there have been major advances in psychotherapeutic and pharmacotherapeutic treatments for substance use disorders. Recent advances in neurobiology have helped to identify major brain circuitry and neurotransmitter systems involved in substance use disorders, allowing for the development of treatments that more specifically target the systems and regions involved in addictive processes. Unfortunately, despite these new developments in medication treatments, medications are

often underused in the treatment of substance use disorders. For example, a large comparison effectiveness study of approximately 41,000 individuals with opioid use disorder reported that only 15% received treatment with one of the FDA-approved medications, although buprenorphine and methadone have been shown to reduce the risk of overdose compared with behavioral interventions and no treatment (Wakeman *et al.* 2020). The lack of access to lifesaving medications for opioid use disorder is a crucial public health issue, given the recent Centers for Disease Control and Prevention (CDC) provisional report indicating a 30% increase in annual drug overdose deaths since the beginning of the 2020 COVID-19 pandemic--largely driven by high-potency synthetic opioids such as fentanyl (Kariisa *et al.* 2022). There are many potential reasons for this increase, including the fact that much of the addiction treatment system has "grown up" outside of traditional medicine, so medications are sometimes not considered in treatment planning. In addition, many treatment programs still do not have the necessary medical personnel to evaluate patients for the appropriateness of medication treatment and prescribe it as needed. Many insurance plans provide little coverage for medications to treat substance use disorders. Broader education of physicians concerning recognition and pharmacological treatment of substance use disorders is clearly needed.

In this chapter, we focus on pharmacotherapeutic treatments for substance use disorders, but we also discuss important advances made in psychotherapeutic and behavioral treatments for these disorders. Although pharmacotherapeutics are an important and sometimes neglected part of the treatment armamentarium, medications alone are rarely sufficient for the treatment of substance use disorders and should be accompanied by comprehensive treatment planning and psychosocial treatment.

In terms of behavioral and psychosocial treatments, a meta-analysis of 34 well-controlled trials of psychosocial therapies included studies of contingency management, relapse prevention, cognitive-behavioral therapy (CBT), and combinations of CBT and contingency management. Contingency management treatments had the lowest dropout rates (< 30%), followed by CBT and combined psychosocial treatments. Treatment involving relapse prevention techniques led to the highest rate of abstinence (39%), and greater time in treatment was related to positive outcomes (Dutra *et al.* 2008). Another study found that CBT, 12-step facilitation, and brief motivational therapy were all efficacious in the treatment of DSM-IV alcohol dependence (American Psychiatric Association 1994; Project MATCH Research Group 1997). In addition, substance use disorders are truly complex and are influenced by biological and psychological factors as well as environmental circumstances. One study comparing standard methadone services with methadone services enhanced by on-site access to medical-psychiatric, employment, and family therapy found that individuals receiving enhanced services showed significantly better outcomes across several functional domains (McLellan *et al.* 1993).

Opioid Use Disorder

Opioid overdose deaths remain one of the most dramatic and deadly public health issues faced in the United States. Over the last 15 years, deaths due to opioid overdose exceeded 500,000, and declines in overall U.S. life expectancy are partially explained by this increase in overdose mortality (Hedegaard *et al.* 2020). This devastating situation has been worsened by the COVID-19 pandemic, and the estimated 70,000 opioid overdose deaths recorded during 2020 mark a 27% increase compared to estimates for 2019, according to preliminary data from the CDC National Center for Health Statistics. Overall, provisional data indicate that more than 109,000 drug overdose deaths were recorded in 2022, the largest number ever recorded in a 12-month period (National Center for health Statistics 2023).

There are three FDA-approved medications for the treatment of opioid use disorder (methadone, buprenorphine, and naltrexone), one recently approved for the treatment of opioid withdrawal symptoms (lofexidine), and one approved for the reversal of opioid overdose (naloxone). All three treatment agents for opioid use disorder bind to m-opioid receptors, but they differ in their pharmacokinetic and pharmacodynamic properties, intrinsic activity at the receptor, and mechanism of action.

Withdrawal and Detoxification

Opioid withdrawal is classified by DSM-5 (American Psychiatric Association 2013) as a condition in which a patient exhibits at least three of the following symptoms after cessation or reduction of opioid use: dysphoric mood; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation, piloerection, or sweating; diarrhea; yawning; fever; or insomnia. Treating opioid withdrawal (detoxification) has traditionally involved short-term substitution therapy followed by abstinence. Opioid withdrawal can begin within 8-12 hours of last use and generally peaks at 24-72 hours, with acute symptoms resolving within 5-7 days; however, the time course is dependent on the half-life of the agent being used. A protracted abstinence syndrome may continue for an additional 6-8 months and includes dysphoria, fatigue, insomnia, and irritability (Martin and Jasinski 1969). Full (methadone) and partial (buprenorphine) opioid agonists and a-adrenergic agents have been used for detoxification. If an individual is not placed on long-standing medication therapy, they are tapered off the medications over the course of 1-4 weeks and encouraged to remain abstinent with continued psychosocial treatment.

In a study comparing taper regimens of 1, 2, and 4 weeks in 70 adults with prescription opioid use disorder, Sigmon *et al.* (2013) found that patients who received the 4-week taper fared better on all outcomes. The 4-week taper group showed greater abstinence rates at week 5 (63% vs. 29% vs. 29%) and week 12 (50% vs. 16% vs. 20%) compared with the 2-and 1-

week taper groups. respectively. The 4-week taper group also had more responders, better retention, and greater post-taper naltrexone ingestion. In a multisite trial, Woody *et al.* (2008) examined taper durations in 152 youths (ages 15-21 years) with opioid use disorder who were randomly assigned to 12 weeks of buprenorphine-naloxone treatment or a 14-day detoxification protocol. Compared with youths receiving the 14-day detoxification regimen, those receiving the 12-week treatment had significantly fewer positive opioid urine test results and higher retention over the 12-week study; however, there were no between-group differences on any outcome measures at 6, 9, and 12 months after treatment. In general, longer taper durations are associated with higher abstinence rates and greater retention in treatment (Dunn *et al.* 2011). Furthermore, a systematic Cochrane Review reported that across studies, heroin-dependent adults who received methadone for detoxification only showed greater illicit heroin use and worse retention compared with those who received methadone for both detoxification and maintenance (Mattick *et al.* 2009).

a_2 Agonists (e.g., clonidine, lofexidine, and guanfacine) have long been used in the treatment of opioid withdrawal. In a Cochrane Review of 26 randomized controlled trials (RCTs) including 1,728 patients, Gowing *et al.* (2014) found that a_2 agonists were more effective than placebo in treating symptoms of opioid withdrawal but caused more adverse events such as hypotension. Whereas lofexidine has been approved for the treatment of opioid withdrawal symptoms in the United Kingdom since 1992, it was only recently approved in the United States for this indication (U.S. Department of Health and Human Services 2018). In a large, multicenter FDA registration trial for the treatment of opioid withdrawal (Fishman *et al.* 2019), participants were assigned to placebo or one of two lofexidine dosages (2.16 or 2.66 mg/day). Although the magnitude of the decrease in opioid withdrawal scores was small, there was a significant difference between lofexidine and placebo, and the authors concluded that lofexidine was safe and effective for the treatment of opioid withdrawal. Three small trials compared clonidine and lofexidine for opioid withdrawal symptoms.

The two agents showed similar efficacy, with more hypotension associated with clonidine (Gowing *et al.* 2014).

Several studies have compared detoxification with a-adrenergic agents to opioid agonist detoxification. Some studies have been unsuccessful or have shown no difference between groups (Gold *et al.* 1978, 1980; Ling *et al.* 2005), and a systematic review found side effects with a-adrenergic agents to be a significant issue (Gowing *et al.* 2003). One RCT (Law *et al.* 2017) compared the combination treatments of buprenorphine-naloxone and methadone-lofexidine for outpatient stabilization and detoxification. All participants showed a rapid reduction in withdrawal symptoms, but the methadone-lofexidine group experienced less craving and greater withdrawal symptoms. In another 14-week trial, clonidine used in conjunction with buprenorphine was associated with a longer duration of opioid abstinence than buprenorphine alone (Kowalczyk *et al.* 2015). The exploration of a-adrenergic agents as adjuncts to opioid agonists in detoxification warrants further investigation.

Rapid detoxification procedures also have been developed, including 1) rapid withdrawal induction with naltrexone, followed by high doses of clonidine and benzodiazepines to attenuate associated symptoms; and 2) rapid withdrawal under general anesthesia, with administration of numerous and varied medications to manage symptoms. These methods generally are not recommended, and rapid withdrawal under general anesthesia has been associated with multiple deaths within 72 hours (~ 3 days) of the procedure (Whittington *et al.* 2000). Although detoxification is important, rapidity should not be emphasized. Given the chronic, relapsing nature of opioid use disorders, first-line treatment has shifted toward lengthier taper durations and maintenance therapy combined with relapse prevention counseling.

Medication-Assisted Treatment

Medication-assisted treatment refers to the use of medications in combination with counseling and behavioral therapies and has demonstrated efficacy in treating opioid use disorder and in achieving sustained recovery (Mattick *et al.* 2014). In the following section, the three medication-assisted treatment modalities (methadone, buprenorphine, and naltrexone) are described.

Methadone

Methadone is a full opioid agonist with high affinity for the m opioid receptor, a long half-life, and delayed steady-state efficacy. Methadone was initially introduced in the United States in 1947, and has been regulated by the federal government as a treatment for opioid use disorder since 1972. Methadone maintenance treatment (MMT) involves closely monitored daily administration by licensed physicians at federally regulated treatment centers. Patients must attend clinic daily unless they earn take-home privileges for meeting clinic criteria such as employment and long-term abstinence. To be started on MMT, patients must be at least age 18 years and must have had an opioid use disorder for at least 1 year. MMT has been the focus of numerous clinical trials, which collectively indicate that it clearly reduces illicit opioid use and improves treatment retention (Fullerton *et al.* 2014; Mattick *et al.* 2009). MMT also has been associated with decreased mortality (Gunne and Gronbladh 1981; Kinlock *et al.* 2007), reduced nonopioid drug use (Faggiano *et al.* 2003), and decreased drug-related HIV risk behaviors (Sees *et al.* 2000). Psychosocial counseling focuses on lifestyle changes (McLellan *et al.* 1993), and interventions such as contingency contracting and voucher incentives can significantly improve outcomes of individuals receiving MMT (Brooner *et al.* 2007).

Initial dosing should begin with methadone 10-20 mg. If withdrawal symptoms are not adequately suppressed within 1 hour, additional medication may be required but should not exceed 30 mg in the first day and 40 mg in the first 3 days. Once withdrawal symptoms are stabilized, dosing can be increased to 100 mg or higher for tolerant individuals. With appropriate administration and adherence, methadone is generally safe. However, methadone-associated risks such as respiratory depression, corrected QT interval prolongation, and sudden death require acute monitoring and led to a 2006 physician safety alert from the FDA. The Substance Abuse and Mental Health Services Administration also issued recommendations for physicians who provide MMT, which include notifying patients of potential cardiac complications, screening patients for cardiac conditions, and, when indicated, conducting a pretreatment and 1-month electrocardiogram (Center for Substance Abuse Treatment 2005).

Buprenorphine

Buprenorphine is a partial opioid agonist with high affinity for the m opioid receptor. Buprenorphine suppresses opioid withdrawal and craving, reduces illicit opioid use, and can block exogenous opioid effects, including respiratory depression (Coe *et al.* 2019). Although buprenorphine also binds the d opioid receptor and is a high-affinity k opioid receptor antagonist, these actions are not likely to play a role in the use of buprenorphine in the treatment of opioid use disorder. When buprenorphine was initially approved, only physicians were allowed to prescribe it to treat opioid use disorder following an 8-hour training and approval from the U.S. Department of Health and Human Services. In 2016, the Comprehensive Addiction Recovery Act permitted nurse practitioners and physician assistants to obtain a waiver to prescribe buprenorphine following a 24-hour training and U.S. Department of Health and Human Services approval, with the goal of increasing access to treatment (Andrilla *et al.* 2018). There are limitations on the number of patients that can be seen depending on the practitioner's degree, experience, and treatment setting.

Both a buprenorphine tablet and a combined buprenorphine and naloxone film for sublingual administration were approved by the FDA in 2002 for the office-based treatment of opioid use disorder. The incorporation of naloxone in buprenorphine products was designed to decrease misuse of these products via intranasal and intravenous routes of administration. Naloxone is a high-affinity m opioid receptor antagonist with a short half-life and rapid dissociation (~ 6.5 min) from the m opioid receptor. When buprenorphine-naloxone is ingested via prescribed routes, naloxone is inert due to poor oral and sublingual bioavailability; however, when taken by the intranasal or intravenous route, naloxone is bioavailable and can precipitate withdrawal.

Given its high affinity and slow dissociation, buprenorphine may induce acute withdrawal if receptors are bound by a full agonist at the time of administration. To avoid precipitating withdrawal, physicians should wait until the patient is experiencing withdrawal symptoms to begin induction with buprenorphine. Initial dosing usually begins with 2-4 mg, which, if well tolerated, can be followed by an additional 2-4 mg approximately 8 hours later. Many patients will require a 24-to 32-mg maintenance dose, but others can be maintained with 16 mg or less once their symptoms are stabilized.

Early trials of buprenorphine established its efficacy in treating opioid use disorders. In a 25-week RCT comparing buprenorphine and methadone, investigators found the two medications to be equally effective in reducing opioid use and retaining participants in treatment (Johnson *et al.* 1992). A systematic Cochrane review evaluated evidence comparing buprenorphine maintenance with MMT and placebo (Mattick *et al.* 2014). Fixed-dose results suggested that compared with placebo, buprenorphine improved treatment retention at any dose but suppressed illicit opioid use only at doses of 16 mg or higher. Buprenorphine did not differ in treatment retention or suppression of opiate use at medium or high doses (7-15 or 16 mg) compared with methadone (40-85 or 85 mg), although low-dose methadone (40 mg) was associated with better retention than low-dose buprenorphine (2-6 mg). Studies using flexible dosing reported that buprenorphine retained fewer participants compared with methadone; however, among those retained in treatment, no difference in the suppression of opioid use was seen.

Weiss *et al.* (2011) conducted a two-phase study with 653 participants and examined brief and extended buprenorphine-naloxone treatment for prescription opioid dependence. Brief treatment included a 2-week stabilization phase, followed by a 2-week taper and an 8-week postmedication follow-up assessment (12-week treatment). The extended treatment condition included 12 weeks of buprenorphine-naloxone treatment, followed by a 4-week taper and an 8-week postmedication follow-up (24-week treatment). Extended treatment produced more successful outcomes, but only while patients were maintained on buprenorphine-naloxone; at the 8-week postmedication follow-up, there were significant reductions in treatment success rates.

Long-acting buprenorphine formulations. Further efforts to reduce diversion, improve adherence, and enhance outcomes include the development of a subcutaneous buprenorphine implant (Probuphine; Titan), which was approved by the FDA in 2016. Probuphine requires an office-based procedure for insertion and removal by trained personnel. The implant consists of four rods, each containing buprenorphine 80 mg (total 320 mg). Studies demonstrated that the implant is superior to placebo and equivalent to sublingual buprenorphine at suppressing withdrawal, decreasing craving, and reducing illicit opioid use (Ling *et al.* 2010; Rosenthal *et al.* 2013, 2016). Implant-site adverse events occurred in 23% (Rosenthal *et al.* 2016) to 56.5% (Ling *et al.* 2010) of subjects. In the outpatient trials, there were no adverse events related to respiratory depression or overdose in the persons receiving implants.

In 2017, the FDA approved a subcutaneous buprenorphine injection (Sublocade) designed for monthly administration that is now available in 100-and 300-mg doses. In trials evaluating the efficacy of the depot to reduce withdrawal, craving, and illicit opioid use, participants with opioid use disorder were inducted onto sublingual buprenorphine for up to 2 weeks and then randomly assigned to six once-monthly injections of 1) depot 300 mg, 2) two 300-mg doses followed by four 100-mg doses, 3) or matched placebo injections (Coe *et al.* 2019). Significantly more patients receiving either active dosing regimen provided illicit opioid-negative urine samples on at least 80% of testing days compared with placebo (28.4% vs. 2% for active dosing vs. placebo). There were no differences in efficacy between the two dosing regimens, but adverse events were more frequent with the higher dose. These findings suggested that the lower dosing regimen is likely appropriate for most patients. Secondary analyses suggested that certain subpopulations (e.g., people who inject drugs) may benefit from the higher-dose regimen.

In 2018, the FDA approved a second injectable, extended-release buprenorphine product that can be given once monthly or once weekly (Brixadi; Braeburn) for the treatment of opioid use disorder (U.S. Food and

Drug Administration 2018). Brixadi demonstrated noninferiority compared with daily sublingual buprenorphine-naloxone in terms of responder rate and superiority to sublingual buprenorphine-naloxone in the percentage of negative opioid urine samples from weeks 4-24. Brixadi is the only injectable buprenorphine studied against standard of care (sublingual buprenorphine-naloxone), with no opioid overdoses in patients receiving Brixadi during clinical trials (Ling *et al.* 2019).

Naltrexone

Naltrexone is a m opioid antagonist that blocks the receptor for 24-72 hours (depending on dose), preventing the experience of drug-induced euphoria. The medication was introduced in addiction treatment in the 1970s as an orally administered nonaddictive medication, with the hope of wide acceptance and effectiveness. However, adherence rates in opioid use disorder are generally low, and overdose due to relapse in previously tolerant individuals poses a serious risk for oral naltrexone use. A Cochrane review reported that most trials with oral naltrexone demonstrate poor outcomes compared with placebo, no treatment, or other pharmacological treatment (Minozzi *et al.* 2011).

Extended-release injectable naltrexone. Extended-release injectable naltrexone is administered in a monthly 380-mg intramuscular injection. The seminal study was a 24-week RCT conducted in Russia with 250 participants (Krupitsky *et al.* 2013), in which participants receiving extended-release naltrexone had a significantly greater median proportion of confirmed weeks abstinent compared with placebo (90% vs. 35%), higher median numbers of opioid-free days (99.2% vs. 60.4%), longer treatment retention (> 168 vs. 96 days), and greater reductions in craving scores. However, extended-release naltrexone inductions can be challenging because of the need for complete detoxification from opioids before starting extended-release naltrexone in order to avoid precipitating withdrawal. In a recent study in opioid use disorder, 72% of participants were successfully inducted onto extended-release naltrexone compared with 94% successfully inducted onto buprenorphine (Lee *et al.* 2018). Once patients were inducted, the relapse rate was comparable for the extended-release naltrexone and buprenorphine groups (52% vs. 56% [Lee *et al.* 2018]).

Recommendations on Medication-Assisted Treatment for Opioid Use Disorder

In summary, methadone seems to be more effective than low-dose buprenorphine in retaining patients in treatment. However, methadone is no different from buprenorphine at higher, fixed doses in terms of treatment retention or suppression of opioid use. Furthermore, the fact that buprenorphine can be obtained via prescription in an office-based practice gives patients and providers more flexibility than is allowed by the regulations surrounding methadone prescribing. The long-acting formulations of buprenorphine have the advantage of improving adherence and decreasing diversion, misuse, and accidental poisoning. However, there is practitioner burden involved in medication administration, particularly for Probuphine. According to a Substance Abuse and Mental Health Services Administration (2012) advisory, subgroups most likely to benefit from extended-release naltrexone include patients whose symptoms were treated unsuccessfully with methadone or buprenorphine, those who prefer a less stigmatizing and more convenient alternative, those opposed to agonist therapy, highly motivated individuals, and adolescents or young adults for whom access to treatment facilities is often restricted by government regulations. In general, oral naltrexone is not recommended because of poor adherence and should be reserved for highly motivated patients who are willing to comply with strategies to improve adherence (e.g., observed dosing).

Novel Medication Approaches to Opioid Use Disorder

N-Methyl-ᴅ-aspartate receptor antagonists, such as memantine, ketamine, dextromethorphan, and phencyclidine, prevent the development of tolerance to and dependence on the analgesic effects of morphine in rodents and play a role in associative opioid reward learning (Herman *et al.* 1995). A recent meta-analysis revealed 19 clinical trials of *N*-methyl-D-aspartate antagonists of varying quality in individuals with opioid use disorder (Fluyau *et al.* 2020). Across the trials, there was moderate evidence showing that these agents reduce opioid withdrawal and modest evidence indicating that they reduce opioid use and craving. Ibogaine, an indole alkaloid derived from root bark, is another novel agent that has been explored in the treatment of opioid use disorder. Ibogaine is classified as a hallucinogen in the United States, but it is unregulated in many countries where it is used in religious and cultural ceremonies (Mash 2018). Animal studies have demonstrated that ibogaine can decrease opioid self-administration. Several uncontrolled observational studies suggest that ibogaine may treat symptoms of opioid withdrawal and have some value in relapse prevention

(Brown and Alper 2018). An exploratory human laboratory trial found that acute administration of cannabidiol (CBD) decreased both craving and anxiety induced by the presentation of opioid-related cues in individuals with opioid use disorder (Hurd *et al.* 2019). These compounds are of interest because they represent novel therapeutic mechanisms, but there is much work to be done in exploring their potential in opioid use disorder treatment, and unintended adverse consequences (e.g., abuse potential) must be considered.

Overdose Treatment

The increasing opioid overdose death rate has led to substantial efforts to expand access to and education about naloxone, an opioid antagonist that is capable of rapidly reversing opioid overdose by decoupling opioids from the opioid receptor and inducing acute withdrawal. Naloxone can be administered via injection or nasal spray and either route is equally effective in reversing opioid overdose. However, naloxone is short acting; if an individual has overdosed on a long-acting opioid, consecutive doses of naloxone may be required and the odds of requiring rescue dosing are higher with the nasal spray than with the injection (Yousefifard *et al.* 2020). Naloxone access has increased in the past 10 years, with multiple states passing immunity laws that enable physicians to prescribe the drug or civilians and first responders to administer the drug without fear of civil, criminal, or professional liability (National Conference of State Legislatures 2017).

Cannabis Use Disorder

Cannabis remains the most commonly used illicit drug in the United States, with more than 31 million past-month users (Substance Abuse and Mental Health Services Administration 2020). One in five individuals who report lifetime cannabis use meet criteria for cannabis use disorder, and age-based prevalence rates of current cannabis use disorder are 5.8% of adults ages 18-25 years, 1.0% of adults age 26 or older, and 4.6% of adolescents ages 12-17 years (Compton *et al.* 2019; Substance Abuse and Mental Health Services Administration (2020). Cannabis use disorder is associated with significant physical and mental health consequences (Hall 2015; Volkow *et al.* 2014), and a higher severity of cannabis use disorder is associated with an exponential increase in treatment utilization (Hasin *et al.* 2016; Kerridge *et al.* 2018). Despite increasing demand, there is a dearth of effective treatment options for cannabis use disorder. Psychosocial interventions show modest efficacy of limited durability, and despite numerous pharmacotherapy trials targeting a range of mechanisms, there are no FDA-approved medications for cannabis use disorder (Kondo *et al.* 2020; Sherman and McRae-Clark 2016). This section discusses pharmacotherapy trials for the treatment of cannabis use disorder, including the most recent and promising developments in the field.

Psychotropic Medications

Early clinical trials investigated a range of psychotropic medications, including antidepressants, anxiolytics, antipsychotics, and mood stabilizers. Certain pharmacotherapeutic agents showed initial promise, particularly in co-occurring affective disorders, whereas others showed deleterious effects. None have demonstrated efficacy for treating cannabis use disorder in large-scale clinical trials.

Antidepressants and Anxiolytics

Serotonin reuptake inhibitors (including selective serotonin reuptake inhibitors) were some of the first candidate medications, as serotonin is implicated in neuropsychiatric behaviors and disorders including anxiety, depression, appetite, cognition, and substance use disorders. A secondary analysis of placebo-controlled trials of fluoxetine for alcohol-dependent adults with depression found reductions in cannabis use frequency and quantity among a subsample of comorbid cannabis users, suggesting the potential utility of serotonin reuptake inhibitors in cannabis use disorder (Cornelius *et al.* 1999). However, this finding was not supported in a subsequent trial in adolescents and young adults with co-occurring depression and cannabis use disorder (Cornelius *et al.* 2010). Subsequent trials of escitalopram (Weinstein *et al.* 2014) and vilazodone (McRae-Clark *et al.* 2016) also failed to improve cannabis outcomes. The nonbenzodiazepine anxiolytic buspirone also drew early attention in a pilot study, which found greater point-prevalence abstinence among treatment completers (McRae-Clark *et al.* 2009). However, a large follow-up trial in adults with cannabis use disorder found no treatment effect; of note, a gender effect indicated worse outcomes among women compared with men (McRae-Clark *et al.* 2015).

Medications that target the dopaminergic and noradrenergic systems have also been studied, as dopamine plays a critical role in mesolimbic reward processing (Tanda *et al.* 1997) and chronic cannabis use is associated with dopaminergic system dysfunction (Bloomfield *et al.* 2016). The catechol O-methyltransferase inhibitor entacapone, which targets synaptic dopamine regulation, was tested in one open-label trial of 36 cannabis-dependent adults (Shafa 2009); cannabis craving was reduced, but cannabis use data were not reported and no follow-up trials have been published. Bupropion, which inhibits the reuptake of norepinephrine and dopamine and has some limited serotonergic activity, was investigated in an RCT exploring sustained-release bupropion, nefazodone, and placebo in

106 cannabis-dependent adults, with no effect of either medication on cannabis use or withdrawal (Carpenter *et al.* 2009). A 12-week clinical trial of venlafaxine for co-occurring cannabis use disorder and depressive disorders engendered higher D-9-tetrahydrocannabinol (THC) levels and lower abstinence rates and did not reduce depressive symptoms compared with placebo (Levin *et al.* 2013). Moreover, the venlafaxine group reported more severe cannabis withdrawal symptoms (Kelly *et al.* 2014).

Cognitive Enhancers

Atomoxetine is a norepinephrine reuptake inhibitor that is FDA approved for the treatment of ADHD. An open-label study of atomoxetine found trend-level reductions in self-reported cannabis use, but no significant increase in biologically confirmed abstinence (Tirado *et al.* 2008). A second study investigated atomoxetine for cannabis use disorder in adults with ADHD and found a reduction in ADHD symptoms but no effect on cannabis use outcomes (McRae-Clark *et al.* 2010).

Mood Stabilizers

Two mood-stabilizing medications have been investigated for treatment of cannabis use disorder. In a 12-week clinical trial with 25 participants, divalproex did not perform better than placebo in achieving cannabis abstinence, reducing use, or decreasing withdrawal symptoms (Levin *et al.* 2004). In another study, lithium reduced cannabis withdrawal in rats by stimulating oxytocin release (Cui *et al.* 2001). In an RCT with 38 adults with cannabis use disorder, lithium did not improve abstinence rates or reduce cannabis use, although it did reduce withdrawal-related symptoms, including nightmares, appetite, and stomachache (Johnston *et al.* 2014).

Anticonvulsants

Gabapentin, an indirect modulator of the GABAergic system, is FDA approved for the treatment of epileptic seizures and neuropathic pain. A small pilot study reported that gabapentin reduced cannabis use and withdrawal symptoms (Mason *et al.* 2012); however, results posted from a larger follow-up study do not suggest an impact on cannabis abstinence (ClinicalTrials.gov NCT00974376). A placebo-controlled trial of topiramate, which acts on GABAergic and glutamatergic systems, in adolescent cannabis users also reported negative results (Miranda *et al.* 2017).

Glutamatergic Modulators

The glutamatergic modulator *N*-acetylcysteine (NAC) received recent attention in two randomized, placebo-controlled clinical trials of NAC versus placebo for the treatment of cannabis use disorder. The first study in 116 young adults ages 13-21 years found significantly greater point-prevalence abstinence rates among participants receiving NAC 1,200 mg/day compared with matching placebo (40.9% vs. 27.2%, respectively) (Gray *et al.* 2012). However, in a subsequent RCT in 302 adults, there were no differences between the NAC and placebo groups in cannabis abstinence, treatment retention, or medication adherence (Gray *et al.* 2017).

Cannabinoids

The endocannabinoid system is involved in a number of neurobiological processes, including reward processing, homeostasis, sleep, feeding, emotion regulation, and stress response, and has been identified as a critical target in the treatment of cannabis use disorder (Martin and McRae-Clark 2020). THC is the primary intoxicating component of the *Cannabis sativa* plant and produces its effects via binding at the cannabinoid CB_1 receptor. Agonist therapy with natural and synthetic THC derivatives has been investigated with promising results.

Dronabinol and Nabilone

Dronabinol is an oral THC formulation that acts as a direct CB_1 agonist. Initial inpatient and outpatient human laboratory studies found that dronabinol reduced withdrawal symptoms (Budney *et al.* 2007; Haney *et al.* 2004) but was associated with abuse liability and decrements in cognitive performance (Vandrey *et al.* 2013). Subsequent cannabis cessation clinical trials found no effect on cannabis abstinence. In a 12-week RCT, dronabinol (40 mg/day) reduced withdrawal symptoms and improved retention but did not produce greater reductions in cannabis use (Levin *et al.* 2011). Another placebo-controlled trial of dronabinol (60 mg/day) combined with lofexidine found no differences from placebo in cannabis use, withdrawal, or retention (Levin *et al.* 2016). Nabilone is a synthetic cannabinoid with potential as an agonist replacement therapy. In a human laboratory study, nabilone more effectively reduced cannabis withdrawal symptoms in adults with cannabis use disorder compared with placebo (Haney *et al.* 2013). However, a randomized controlled pilot study did not demonstrate efficacy of nabilone in achieving cannabis abstinence (Hill *et al.* 2017). Given concerns about abuse liability and more recent promising options, dronabinol and nabilone demonstrate low potential for cannabis cessation treatment.

Nabiximols

Agonist replacement therapy using nabiximols, which combines THC with CBD and terpenoids derived from the cannabis plant, has shown promise in recent trials. In an initial study comparing a 6-day course of nabiximols with placebo in 51 inpatients with cannabis use disorder (Allsop *et al.* 2014), nabiximols reduced cannabis withdrawal severity and improved treatment retention but did not significantly reduce cannabis use or time to relapse following treatment. In a 12-week RCT, nabiximols reduced cannabis craving compared with placebo but did not show a treatment effect on cannabis use or withdrawal symptoms (Trigo *et al.* 2018). More recently, a larger RCT with 128 participants demonstrated a reduction in self-reported cannabis use days during treatment with nabiximols (Lintzeris *et al.* 2019) and at a 3-month follow-up (Lintzeris *et al.* 2020), although cannabis withdrawal and psychosocial outcomes did not differ between groups.

Cannabidiol

Human laboratory studies suggest that CBD may mitigate adverse acute effects of THC (for review, see Freeman *et al.* 2019), which has led to investigations of CBD as a potential pharmacotherapeutic agent. In a 10-week open-label trial of CBD 200 mg among 20 heavy cannabis users, participants showed decreased depressive and psychotic symptoms and improved cognitive function after treatment compared with baseline; however, they also reported increased euphoria when smoking cannabis (Solowij *et al.* 2018). A recent 4-week adaptive trial with 48 participants found that compared with placebo, 400-and 800-mg doses of CBD resulted in lower THC/creatinine ratios and an increase in self-reported abstinence, whereas a 200-mg dose did not produce a treatment effect (Freeman *et al.* 2020). Although these studies have notable limitations, including the lack of a control condition, small sample sizes, and brief treatment durations, further investigation of CBD is warranted.

Fatty Acid Amide Hydrolase Inhibitors

Fatty acid amide hydrolase (FAAH) inhibitors are a promising area of medication development for the treatment of cannabis use disorder. The FAAH enzyme breaks down the endocannabinoid anandamide, and evidence suggests that potentiating endocannabinoid signaling through inhibition of anandamide breakdown may reduce withdrawal symptoms (Falenski *et al.* 2010) and decrease risk for cannabis use disorder (Boileau *et al.* 2016). A recent randomized clinical trial in 70 men with DSM-IV cannabis dependence investigated a 3-week course of the FAAH inhibitor PF-04457845 compared with placebo following an inpatient detoxification period (D'Souza *et al.* 2019). Compared with the 24 placebo-treated participants, the 46 participants who received PF-04457845 demonstrated fewer withdrawal symptoms and better sleep during the inpatient phase and lower urinary THC levels and reduced cannabis use during the outpatient phase. A multisite clinical trial of PF-04457845 is currently underway (NCT03386487).

To date, the FDA has not approved any pharmacotherapies for the treatment of cannabis use disorder. Although early studies of psychotropic medications yielded few positive effects, more recent studies of potential agonist replacement therapies, FAAH inhibitors, and CBD have shown promise and may warrant additional investigation.

Tobacco Use Disorder

Despite early declines, the 2019 National Survey on Drug Use and Health reported that 58.1 million people (or 21% of the population ages [?] 12 years) were current users of a tobacco product, with 26.8 million reporting daily cigarette smoking (Substance Abuse and Mental Health Services Administration 2020). Few tobacco users are successful in permanently quitting in their initial attempt; most consume tobacco for many years and cycle through periods of abstinence and relapse. Failure to grasp the chronic nature of tobacco use disorders can lead to discouragement among health care providers and impede treatment over time. In 2018, although about 55% of adult smokers reported a past-year quit attempt, only 7.5% successfully quit (Creamer *et al.* 2019). Counseling strategies, including in-person counseling, telephone quitlines, and self-help materials, have a small but important effect in achieving smoking cessation. Telephone counseling is readily available in the United States through the publicly funded quitline 1-800-QUIT-NOW (1-800-784-8669). A pooled estimate of 47 trials indicated that increasing the amount of behavioral support increased the chance of successful smoking cessation by 10%-25% (Stead *et al.* 2015).

Current practice guidelines recommend the use of an effective medication at every quit attempt unless medically contraindicated or within special populations (e.g., pregnant women, adolescents) for which there is limited evidence of effectiveness (Fiore *et al.* 2008). Seven first-line medications are safe, effective, and FDA approved for smoking cessation, including nicotine replacement therapies (NRTs; patch, gum, lozenge, nasal spray, and inhaler), sustained-release bupropion, and varenicline. Generally, cessation medications double the quit rate relative to placebo (20% vs. 10% [Cahill *et al.* 2013]).

Nicotine Replacement Therapies

NRTs partially replace the nicotine obtained from cigarettes and are intended to aid in quitting by reducing the severity of nicotine withdrawal. A 2012 Cochrane review of 150 studies reported that NRT increased cessation rates to 17% compared with 10% with placebo (number needed to treat = 15 [Stead *et al.* 2012]). Nicotine patches, gum, and lozenges are available over the counter. The nicotine inhaler and nasal spray are prescription medications. Nicotine from the gum and lozenge is absorbed through the buccal mucosa. Nicotine from the inhaler and nasal spray is absorbed through the oropharynx and nasal mucosa, respectively. The nicotine patch, which is designed for skin absorption, has the advantage of once-a-day application and has higher adherence rates as a result.

Nicotine gum is available in 2-and 4-mg doses, with 4-mg nicotine gum recommended for individuals who smoke 25 or more cigarettes a day. Smokers should be instructed to use 1 piece of gum every 1-2 hours (maximum of 24 pieces per day) for the first 6 weeks and to taper the frequency over the next 6 weeks. The gum should be slowly chewed until a "peppery" taste emerges and then "parked" between the cheek and the gum to facilitate absorption. The gum should be intermittently chewed slowly and parked until the taste dissipates, typically in about 30 minutes. Common side effects include hiccups, dyspepsia, and jaw discomfort.

Nicotine lozenges are available in 2-and 4-mg doses, with the 4-mg dose recommended for individuals who smoke their first cigarette within 30 minutes of awakening. In general, at least 9 lozenges per day should be used for the first 6 weeks, with a maximum of 20 lozenges per day. Common adverse effects include hiccups, nausea, and heartburn.

The nicotine patch has the advantage of daily dosing, thus enhancing compliance. For patients who smoke more than 10 cigarettes a day, a standard course includes 21 mg for 6 weeks, followed by 14 mg for 2 weeks, and then 7 mg for 2 weeks. Approximately 50% of patients will experience a mild local skin reaction (Fiore *et al.* 2008), which requires discontinuation in about 5% of patients. Rotating the site daily can help prevent skin reactions. Insomnia and vivid dreams also may occur; removing the patch before bedtime can reduce the disruption in sleep.

Most of the nicotine (4 mg) in an inhaler cartridge is deposited in the mouth, with less than 5% reaching the lower respiratory tract. Puffing intensively (80 deep inhalations over 20 minutes) leads to the absorption of approximately 2 mg. Recommended dosing is 6-16 cartridges a day for 3 months, followed by tapering over the subsequent 3 months. Coughing and rhinitis are common side effects. Exacerbation of reactive airway disease can occur.

The nicotine nasal spray produces the highest nicotine level compared with other forms of NRT. The first dose is 0.5 mg administered in each nostril (total 1 mg) per hour as needed, with a minimum of 8 doses and a maximum of 40 doses per day. The recommended duration of therapy is 3-6 months. Most patients experience varying degrees of nasal irritation. Other common side effects include transient changes in sense of taste and smell. Severe reactive airway disease is a contraindication.

Of note, the use of NRT is not an independent risk factor for acute myocardial infarction. However, NRT should be used with caution in patients who have unstable angina pectoris or severe arrhythmias and who have experienced myocardial infarction within the past 2 weeks. Some smokers may benefit from a longer course of NRT treatment. Schnoll *et al.* (2015) compared 8 weeks (standard), 24 weeks (extended), and 52 weeks (maintenance) of nicotine patch treatment in combination with 12 weeks of smoking cessation counseling. At 6 months, 22% of participants in the standard treatment group were abstinent compared with 27% in the extended and maintenance groups.

Sustained-Release Bupropion

In the late 1990s, the sustained-release formulation of bupropion was FDA approved for smoking cessation and marketed under the trade name Zyban (GlaxoSmithKline). Sustained-release bupropion is an antidepressant with noradrenergic and dopaminergic effects and antagonist action at the nicotinic acetylcholine receptor. In a recent Cochrane review, bupropion was found with high certainty to increase long-term smoking cessation rates for at least 6 months (risk ratio, 1.64) compared with placebo; bupropion may work by blocking nicotine effects, relieving withdrawal, or decreasing depressed mood (Howes *et al.* 2020). A standard sustained-release bupropion course begins with one 150-mg tablet taken by mouth once a day for 3 days, at which point the dosage is increased to one tablet taken by mouth twice a day (separated by at least 8 hours) for 7-12 weeks. The tobacco quit date is 1 week after starting medication. If the treatment is successful, some patients benefit from continued treatment for up to 6 months to prevent relapse.

Sustained-release bupropion is generally well tolerated but lowers the seizure threshold, and seizures are estimated to occur in 1 of 1,000 treated patients (Hughes *et al.* 2014). Contraindications include seizure disorders, eating disorders, and monoamine oxidase inhibitor use within 14 days.

Varenicline

Varenicline is a partial agonist at the a4b2 nicotinic receptor that relieves symptoms of nicotine withdrawal and blocks nicotine from attaching to the receptor, thus reducing the rewarding properties of smoking (Coe *et al.* 2005). Numerous controlled studies support the efficacy of varenicline for smoking cessation. Two 12-week RCTs including more than 2,000 participants (Gonzales *et al.* 2006; Jorenby *et al.* 2006) compared varenicline, bupropion, and placebo. The investigators found that rates of continuous abstinence for the last month of the treatment phase were 44% for varenicline, 30% for bupropion, and 18% for placebo. Continuous abstinence rates at 1 year were 23%, 14.6%, and 10.3% for varenicline, bupropion, and placebo, respectively (Jorenby *et al.* 2006). A standard course is typically 0.5 mg/day for 3 days, then 0.5 mg bid for 4 days, and then 1 mg bid with food. The target quit date is 1 week after starting varenicline. If clinically warranted, the initial total 12-week course can be continued for an additional 12 weeks if initial treatment is successful.

Black Box Warning Removal

In 2009, a black box warning was added to the packaging information for both varenicline and bupropion after an FDA review of postmarketing data concluded that these medications could potentially increase the risk of depression, suicidality, agitation, worsening preexisting psychiatric illnesses, and changes in behavior (U.S. Food and Drug Administration 2009). These warnings call for close monitoring for symptoms or changes in behavior. A 2015 meta-analysis of 39 RCTs with approximately 11,000 participants found no evidence of an increased risk of suicide, suicide attempts, suicidal thoughts, depression, aggression, or death in participants taking varenicline compared with placebo (Thomas *et al.* 2015), confirming results of an earlier meta-analysis by Gibbons and Mann (2013) that included 17 RCTs conducted by Pfizer and a large dataset from the U.S. Department of Defense. In December 2016, the FDA determined that the risk of these serious side effects on mood, behavior, and thinking was lower than expected and the black box warning was removed.

Combination Therapies

A Cochrane review found insufficient evidence to establish whether combined bupropion and NRT result in superior quit rates compared with NRT alone. Previous research has indicated that combination NRT (patch and lozenge) increased quit rates compared with either placebo or monotherapy (Piper *et al.* 2009).

Varenicline combined with bupropion has been investigated in several RCTs. One showed greater 4-week smoking abstinence for weeks 8-11 with combination therapy than with monotherapy (39.8% vs. 25.9%; odds ratio, 1.89 [95% CI, 1.07-3.35]) (Rose and Behm 2014). Ebbert *et al.* (2014) found greater prolonged abstinence (53% vs. 43% at 12 weeks and 37% vs. 28% at 26 weeks) in the combination group compared with varenicline plus placebo, although the results were not significant at 52 weeks. In a study by Rose and Behm (2014), smokers who used the nicotine patch and did not reduce smoking were randomly assigned to 12 weeks of varenicline and sustained-release bupropion or varenicline plus placebo. Participants receiving the combination had significantly higher abstinence rates compared with the varenicline plus placebo group (40% vs. 26%). The combination treatment was significantly more effective in male individuals and highly dependent smokers. Despite these early promising reports, a recent Cochrane meta-analysis found insufficient evidence to determine whether the combination of varenicline and bupropion produced quit rates superior to those seen with varenicline alone (Howes *et al.* 2020).

Second-Line Medications

Second-line medications should be considered on a case-by-case basis if first-line medications (alone or in combination) are ineffective or contraindicated. Several medications are effective but have a more limited role because of potential side effects and lack of FDA approval for smoking cessation. Medications in this category include clonidine and nortriptyline (Fiore *et al.* 2008).

Special Populations

Women Who Are Pregnant or Trying to Conceive

The harmful effects of smoking during pregnancy are well known and include small-for-gestational-age neonates, stillbirth, preterm birth, and placenta previa (Jauniaux and Burton 2007). Current guidelines recommend the use of in-person psychosocial strategies exceeding minimal advice to quit smoking. Although quitting smoking during the first trimester will produce the greatest benefit, quitting at any time is beneficial. In a recent meta-analysis that excluded potentially biased, noncontrolled RCTs, NRT was no more effective than placebo (Coleman *et al.* 2015). Evidence is insufficient to recommend the use of bupropion or varenicline during pregnancy.

Children and Adolescents

Tobacco use is typically initiated and established during adolescence (U.S. Department of Health and Human Services 2012). The annual Monitoring the Future survey has shown a long and significant decline in adolescent cigarette smoking since the mid-1990s, with the lack of a further decrease first occurring in 2020 (Johnston *et al.* 2021). The most critical finding of the latest survey is that vaping has doubled or tripled among eighth-, tenth-, and twelfth-graders. For example, among twelfth-graders, the 30-day prevalence rate of nicotine vaping rose from 11% in 2017 to 26% in 2019 (Johnston *et al.* 2021). Current treatment guidelines recommend that clinicians assess tobacco use in children and adolescents and strongly recommend abstinence. Psychosocial interventions, especially

those that contain CBT components, were efficacious in the short term for the treatment of adolescent smokers (Simon *et al.* 2015). Contingency management and motivational interviewing have shown some effectiveness as stand-alone treatments, and strategies that include elements of the transtheoretical model of change also have shown promise.

Individuals With Comorbid Psychiatric Disorders

Despite the significant decline in smoking rates in the general population, comparable declines in smoking rates among smokers with psychiatric disorders have not been realized. According to combined data from the 2019 National Survey on Drug Use and Health, 21% of adults had some form of mental illness in the past year; of these, 27% were current smokers compared with 16% of adults without mental illness (Substance Abuse and Mental Health Services Administration 2020). Unfortunately, individuals with mental illnesses are frequently excluded from clinical studies focused on the treatment of tobacco use disorders, and smoking cessation therapies are not routinely offered to patients with severe mental illness. Mental health professionals commonly have permissive attitudes toward smoking and mistakenly assume that patients with comorbid psychiatric and substance use disorders are not interested in quitting (Sheals *et al.* 2016). These attitudes and misconceptions undermine the provision of smoking cessation interventions in these populations.

Evidence shows that smoking cessation therapies are both effective and well tolerated in populations with severe mental illness. A recent large multisite, global smoking cessation trial of more than 4,000 participants compared the efficacy and safety of NRT, bupropion, and varenicline in individuals with mood, psychotic, and anxiety disorders (Evins *et al.* 2019). Neither varenicline nor bupropion was associated with a higher rate of severe neuropsychiatric adverse events relative to NRT or placebo. Similar to previous studies of smokers without a mental disorder, varenicline was superior to bupropion, NRT, and placebo and both bupropion and NRT were superior to placebo. These results indicate that pharmacotherapy should be considered in planning smoking quit attempts in psychiatric populations. Clinical practice guidelines recommend a treatment duration of 12 weeks, but more recent evidence indicates that maintenance pharmacotherapy for 1 year may improve sustained abstinence rates in individuals with schizophrenia spectrum disorders (Evins and Cather 2015).

Admission to a smoke-free psychiatric hospital is a natural opportunity to provide smoking cessation treatment. In a previous study, daily smokers with and without an intention to quit were recruited from several locked psychiatric units and randomly assigned to interventions that included tailored counseling with an emphasis on readiness to quit and NRT availability after discharge (Schuck *et al.* 2016). An impressive 76% of eligible smokers enrolled; of these, 88% requested study-provided NRT. Those with more severe psychiatric symptoms were more likely to request NRT after hospitalization ($P < 0.01$). Participants who requested NRT at discharge were more likely to make a 24-hour quit attempt and to self-report abstinence at the 1-week follow-up (54% with a quit attempt, 14% abstinent) compared with participants who did not request NRT at discharge (25% with a quit attempt, 4% abstinent) ($P < 0.05$).

Individuals With Comorbid Substance Use Disorders

Individuals with other substance use disorders smoke at a higher rate than those without other substance use disorders (56% vs. 21%) and have lower quit rates (23% vs. 51%)

(Streck *et al.* 2020). Importantly, individuals receiving treatment for substance use disorders are more likely to die from smoking-related illnesses than from complications from drug use (Baca and Yahne 2009). However, many individuals receiving substance use disorder treatment continue to smoke despite achieving abstinence from alcohol and drugs (McClure *et al.* 2015). Current treatment guidelines recommend that patients with substance use disorders be offered smoking cessation treatment (Fiore *et al.* 2008). It has been suggested that varenicline may be the most effective treatment for alcohol use disorders and comorbid alcohol and tobacco use disorders, because alcohol produces activation in the mesolimbic pathway through its effects on nicotinic acetylcholine receptors (Soderpalm *et al.* 2000). Varenicline has been reported to decrease alcohol craving and consumption in smoking cessation trials (Fucito *et al.* 2011; Mitchell *et al.* 2012).

In a review of smoking cessation interventions during substance use disorder treatment, a variety of pharmacotherapy and behavioral treatment options significantly improved smoking outcomes (Thurgood *et al.* 2015). Smokers with opioid use disorders may present a particular challenge. Smoking rates among individuals with opioid use disorder are fourfold higher than among the general population, and recent pharmacotherapy outcomes have been disappointing and typically worse than those seen in the general population (Miller and Sigmon 2015). Additional research to understand the relationship between tobacco and substance use disorders is warranted, given that smoking cessation has the potential to improve the morbidity and mortality associated with these common disorders.

Stimulant Use Disorder

The search for a pharmacotherapeutic treatment for cocaine and amphetamine use disorders has been extremely active over the last 20 years, with controlled trials of antidepressants, anticonvulsants, dopamine agonists and antagonists, and many other agents. Unfortunately, many medications that show promise in animal models of stimulant dependence and/or positive outcomes in small uncontrolled trials fail to decrease drug use by objective measures in larger controlled trials. In addition, many clinical trials in stimulant-dependent individuals have high dropout rates and medication noncompliance. To date, there are no FDA-approved medications for the treatment of cocaine or amphetamine use disorders; however, the medications discussed in this section have shown promise, often in subgroups of individuals studied.

Agonist Replacement Strategies

As discussed in previous sections, agonist replacement therapies are effective in nicotine and opioid use disorders. For this reason, the focus of many studies in stimulant use disorder treatment has been agonist replacement in which a pharmacologically similar agent is substituted for the stimulant of abuse. An ideal agonist replacement therapy for stimulant dependence should share some pharmacological and behavioral effects with cocaine or amphetamine but have less abuse potential. Unfortunately, many agents that have shown promise do not meet these criteria.

Methylphenidate, an agent that produces effects similar to those of cocaine at the dopamine transporter and is approved for the treatment of ADHD, has been tested in cocaine and amphetamine use disorder in patients with and without ADHD. Although the results of these studies have generally been negative (Stoops and Rush 2013), findings have been mixed in individuals with ADHD, with positive results seen in cocaine and amphetamine use disorder with a dosage of 60 mg/day (Konstenius *et al.* 2010; Levin *et al.* 2007) and negative results seen in cocaine use disorder with 80-90 mg/day (Levin *et al.* 2006; Schubiner *et al.* 2002). Several trials have indicated that D-amphetamine and methamphetamine can decrease cocaine use in individuals with cocaine use disorder (Grabowski *et al.* 2001, 2004; Mooney *et al.* 2009; Shearer *et al.* 2003). However, trials of D-amphetamine in amphetamine use disorder have been negative (Galloway *et al.* 2011; Longo *et al.* 2010). These studies suggest that stimulant replacement warrants further investigation, but it must be noted that the abuse and diversion potential of methylphenidate and amphetamines limits the potential widespread utility of this approach (Stoops *et al.* 2004).

Other Pharmacotherapeutic Agents

Bupropion

Bupropion, an antidepressant with dopaminergic activity, has been tested in multiple clinical trials in both cocaine and methamphetamine use disorders. The results were largely mixed, but bupropion seems to have some efficacy when combined with consistent behavioral treatment for patients with cocaine use disorder (Poling *et al.* 2006) and in methamphetamine users with less severe methamphetamine use disorder (Elkashef *et al.* 2008; Shoptaw *et al.* 2008). A recent double-blind, placebo-controlled trial explored the use of extended-release injectable naltrexone plus oral extended-release bupropion in methamphetamine use disorder in a two-stage design, in which individuals taking placebo who did not have a response in the first 6 weeks were randomly reassigned to treatment (Trivedi *et al.* 2021). Response was defined as at least three of four methamphetamine-negative urine samples at the end of stage 1 or 2. The weighted average response across the two stages was 13.6% with naltrexone-bupropion and 2.5% with placebo ($P < 0.001$). Although the response rate for active treatment was low, there was a significant difference from placebo.

Disulfiram

In addition to its effects on alcohol metabolism, disulfiram blocks the enzymatic degradation of both cocaine and dopamine. Investigators have hypothesized that increased dopamine levels may help improve hedonic tone (i.e., sense of well-being, pleasure, or contentment) in individuals with cocaine use disorder, and increased cocaine levels have been shown to increase cocaine-related anxiety and dysphoria in individuals pretreated with disulfiram (Hameedi *et al.* 1995). Regardless of the mechanism, four clinical trials to date have reported that disulfiram reduces cocaine use in individuals with cocaine use disorder (Carroll *et al.* 2004; George *et al.*

2000). Given these results, disulfiram should be considered in the treatment of cocaine use disorder as long as the individual is willing to remain alcohol free and understands the potential for increased toxicity with cocaine use.

Modafinil

Modafinil, a glutamatergic agent that is FDA approved for narcolepsy, has been tested in both cocaine and amphetamine use disorders. Although initial trials were positive (Dackis *et al.* 2005), subsequent trials reported that efficacy was limited to individuals

who did not have a history of alcohol use disorder and to men (Anderson *et al.* 2009; Dackis *et al.* 2012). Trials of modafinil are ongoing, but the medication is well tolerated and may be useful in reducing cocaine withdrawal symptoms and helping some individuals attain abstinence (Malcolm *et al.* 2002).

Topiramate

There have also been several promising studies with topiramate, an anticonvulsant agent that has shown promise in alcohol use disorder. In one placebo-controlled trial of cocaine dependence, topiramate-treated subjects were more likely than placebo-treated subjects to achieve 3 weeks of continuous abstinence and to be rated as clinically improved (Kampman *et al.* 2004).

Vigabatrin

Vigabatrin (g-vinyl-GABA), an anticonvulsant that increases GABA neurotransmission by inhibiting GABA transaminase, showed promise in several open-label trials in cocaine and methamphetamine use disorders. A placebo-controlled trial reported higher rates of abstinence (assessed by self-report and urine drug screen) in the vigabatrin-treated group with cocaine use disorder than in the placebo group (Brodie *et al.* 2009), whereas a multisite trial (Somoza *et al.* 2013) found no difference in any outcomes in individuals with cocaine use disorder taking vigabatrin compared with placebo. However, compliance with vigabatrin was low in the trial by Somoza *et al.* (2013), which calls the negative results into question.

N-Acetylcysteine

N-Acetylcysteine is a glutamatergic agent that also has shown consistent positive results in animal models of cocaine use disorder (Baker *et al.* 2003). Although an initial pilot study with a crossover design showed promise in cocaine use disorder (LaRowe *et al.* 2006), a follow-up double-blind, placebo-controlled trial (LaRowe *et al.* 2013) reported no difference between two doses of *N*-acetylcysteine and placebo on any outcome measures. However, a reduction in cocaine-positive urine drug screens was seen in a small subset of individuals who were abstinent at initiation of study drug, suggesting that *N*-acetylcysteine may be more efficacious in preventing relapse than in initiating abstinence. Further studies are required to assess this possibility.

Conclusion and Future Directions

Effective pharmacological treatments are available for opioid and tobacco use disorders, but studies suggest that these treatments are underutilized and there is clearly room for improvement in terms of efficacy. Exploration of medications with novel mechanisms of action, including hallucinogens, is ongoing for both tobacco and opioids, but much work remains to be done. The search for medication treatment for stimulant use disorders remains an active area of research, with a wide range of agents being tested across hundreds of clinical trials. To date, the FDA has not approved any pharmacotherapies for the treatment of cannabis use disorder, but recent studies of potential agonist replacement therapies, FAAH inhibitors, and CBD have shown promise and may warrant additional investigation. Given the devastating personal and societal effects of substance-related disorders, pharmacotherapy should be considered when appropriate as part of a comprehensive treatment plan.

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CHAPTER 55

Treatment of Alcohol Use Disorder

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Introduction

Epidemiology of Alcohol Misuse

A 2021 national survey found that approximately 28.6 million Americans (11.3%) met DSM-5 (American Psychiatric Association 2013) criteria for alcohol use disorder (AUD) (Substance Abuse and Mental Health Services Administration 2021a). Alcohol misuse was estimated to cost the U.S. economy about $249 billion annually, on the basis of factors such as lost productivity, health care expenses, and law enforcement costs (U.S. Department of Health and Human Services 2016). About three-quarters of alcohol-related costs to U.S. society are due to *binge drinking*--defined as a pattern of drinking that raises the blood alcohol concentration (BAC) to 0.08% (i.e., 0.08 grams of alcohol per deciliter (g/dL) or higher (Figure 55-1). This pattern corresponds to consumption of 4 or more (for women) or 5 or more (for men) *standard drinks* (Figure 55-2) within a 2-hour time frame. Such alcohol misuse is associated with harm to drinkers and those around them, increasing the risk of motor vehicle crashes, unsafe sexual behavior, suicidality, alcohol overdose, and fetal alcohol spectrum disorders.

Chronic *heavy drinking*--defined as regular consumption of 4 or more drinks per day or more than 7 drinks per week for women, and 5 or more drinks per day or more than 14 drinks per week for men--is causally associated with various cancers, heart disease, liver disease, depression, and cognitive deficits (National Institute on Alcohol Abuse and Alcoholism 2023). Alcohol is responsible for the deaths of more than 140,000 Americans annually (Centers for Disease Control and Prevention 2020; National Institute on Alcohol Abuse and Alcoholism 2023), with over 82,000 deaths due to chronic conditions such as liver disease, and over 58,000 deaths due to acute causes such as accidents. Alcohol consumption accounts for about half of all liver disease in the United States (Yoon and Chen 2018), and more than 10,000 people die from drunk driving every year, including victims who were not using alcohol (National Center for Statistics and Analysis 2020). Worldwide, alcohol misuse is the seventh leading risk factor for premature death and disability (Global Burden of Disease 2016 Alcohol Collaborators 2016).

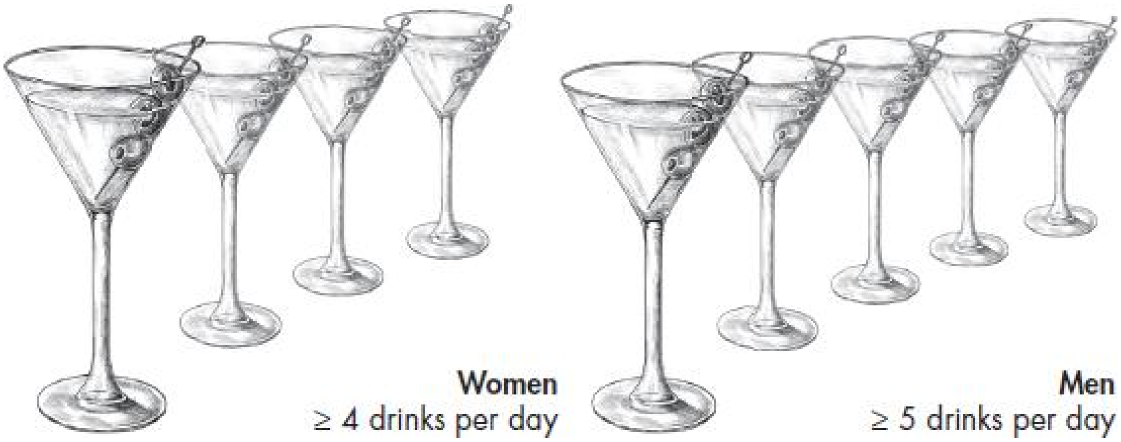

FIGURE 55-1. Heavy drinking and binge drinking.

Heavy drinking is defined as 4 or more standard drinks per day for women, and 5 or more standard drinks per day for men. *Binge drinking* is defined as a pattern of drinking that raises the blood alcohol concentration to 0.08% or higher.

Source. National Institute on Alcohol Abuse and Alcoholism (NIAAA): *Rethinking Drinking: Alcohol and Your Health* (NIH Publication No. 21-AA-3770). Bethesda, MD, NIAAA, July 2022b. Available at: https://www.niaaa.nih.gov/sites/default/files/publications/NIAAA_RethinkingDrinking.pdf. Accessed April 23, 2023.

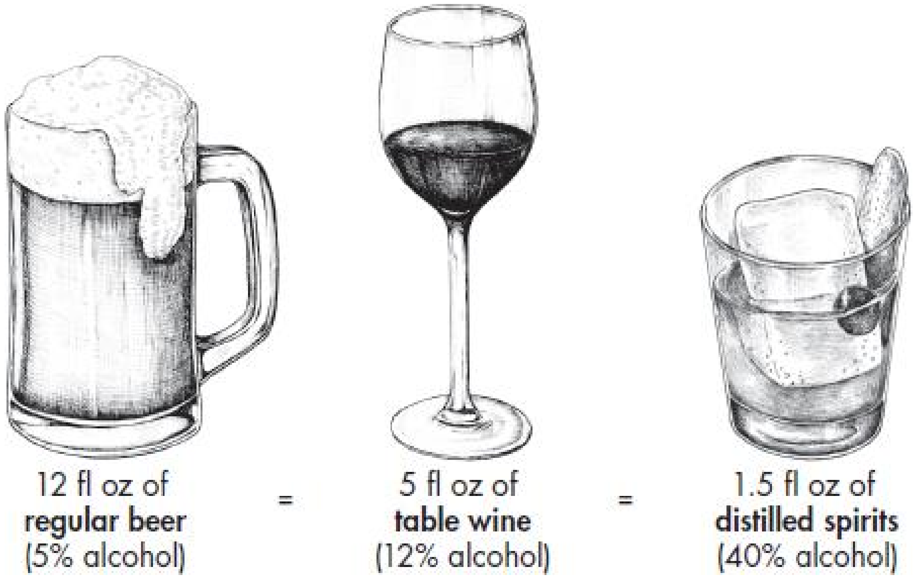

FIGURE 55-2. Standard drink equivalents.

In the United States, a *standard drink* is defined as any drink that contains about 0.6 fluid ounces, or 14 grams, of pure alcohol. This amount of alcohol roughly corresponds to 12 ounces of regular beer (usually about 5% alcohol), 5 ounces of wine (usually about 12% alcohol). and 1.5 ounces of distilled spirits (usually about 40% alcohol [i.e., 80 proof]). Although standard drink amounts are helpful for following health guidelines and monitoring alcohol use, they may not reflect customary serving sizes.

Source. National Institute on Alcohol Abuse and Alcoholism (NIAAA): *Rethinking Drinking: Alcohol and Your Health* (NIH Publication No. 21-AA-3770). Bethesda, MD, NIAAA, July 2022b. Available at: https://www.niaaa.nih.gov/sites/default/files/publications/NIAAA_RethinkingDrinking.pdf. Accessed April 23, 2023.

Detection and Diagnosis of Alcohol Use Disorder

A common reason why individuals with AUD do not seek treatment is that they are unaware that they need it (U.S. Department of Health and Human Services 2016). Individuals may never have been told that they have AUD or may not consider themselves to have a drinking problem. Underestimating the severity of one's drinking problem and overestimating one's ability to control it are associated with alcohol-induced changes in brain circuits that control incentive salience, negative affect, and executive function (Koob and Le Moal 1997; U.S. Department of Health and Human Services 2016). These factors underscore the importance of adequate screening and accurate diagnosis as a first step in treating AUD. The Screening, Brief Intervention, and Referral to Treatment (SBIRT; Substance Abuse and Mental Health

Services Administration 2013) model is an evidence-based approach to early detection and intervention for those at risk for developing AUD. The SBIRT model makes efficient use of a clinician's time, which may be particularly important when multiple potential disorders require assessment. For example, a single standardized screening question was found to effectively detect unhealthy alcohol use: "How many times in the past year have you had X or more drinks in a day?" where X is 5 for men and 4 for women, and a response of 1 or greater is considered positive (Smith *et al.* 2009). Quick questions on drinking quantity and frequency do not provide a diagnosis of AUD. However, a positive screen can serve as a signal that further evaluation is warranted because chronic heavy alcohol use may lead to the development of AUD. For individuals found to be drinking at an unhealthy level, the SBIRT model stipulates that a brief intervention using motivational interviewing be provided. A Cochrane Review concluded that brief interventions were more effective in reducing alcohol consumption compared with control conditions at follow-up 1 year after the brief intervention (mean difference -20 g/week), with comparable efficacy found in men and women (Beyer *et al.* 2019). If clinical follow-up shows that the brief intervention was ineffective in reducing alcohol use, evidence-based pharmacological and behavioral treatment for AUD should be provided.

A diagnosis of AUD is based on positive findings on at least 2 of 11 DSM-5 criteria, as shown in Table 55-1. DSM-5 combines earlier diagnostic criteria for alcohol abuse and dependence under the term *alcohol use disorder*, with severity modifiers of *mild*, *moderate*, or *severe* based on the number of criteria met. ICD-11 (World Health Organization 2021), ICD-10 (World Health Organization 1992), and DSM-IV (American Psychiatric Association 1994) use the term *alcohol dependence* and include congruent diagnostic criteria (Degenhardt *et al.* 2019; Lago *et al.* 2016). DSM-5 criteria for AUD of moderate or greater severity were found to be essentially equivalent to DSM-IV and ICD-10 criteria for alcohol dependence (Compton *et al.* 2013). Pharmacological treatment is typically considered for alcohol dependence and AUD of moderate or greater severity. This stage of the disorder usually follows a chronic, relapsing course characterized by compulsive heavy alcohol drinking despite harmful consequences that may be mitigated by pharmacological treatment (American Psychiatric Association 2013, 2017).

TABLE 55-1. Summary of DSM-5 criteria for alcohol use disorder and ICD-11 criteria for alcohol dependence

DSM-5 criteria for alcohol use disorder (APA 2013)	ICD-11 criteria for alcohol dependence (WHO 2021)
A problematic pattern of alcohol use manifested by [?] 2 symptoms within 12 months:	A problematic pattern of alcohol use manifested by [?] 2 symptoms of impaired regulation:
1. Impaired control over use	1. Impaired control over use
2. Unsuccessful efforts to cut down or quit	2. Alcohol use prioritized over other aspects of life despite negative consequences
3. Extensive time spent drinking or recovering from drinking	3. Physiological indicators of neuroadaptation, e.g.,
4. Craving or a strong urge to use	a. tolerance
5. Use given priority over major role obligations	b. withdrawal
6. Use despite interpersonal consequences	c. use of alcohol to prevent or alleviate withdrawal
7. Activities reduced or given up due to use	Symptoms are usually present for 12 months, or 3 months if use is continuous.

Note. Pharmacological treatment is typically indicated for alcohol use disorder of moderate or greater severity and alcohol dependence. APA = American Psychiatric Association; WHO = World Health Organization.

DSM-5 criteria for alcohol use disorder (APA 2013)	**ICD-11 criteria for alcohol dependence (WHO 2021)**
8. Use in physically hazardous situations	
9. Use despite negative health (mental and physical) consequences	
10. Tolerance	
11. Withdrawal	
Current severity:	
Mild: 2 or 3 symptoms	
Moderate: 4 or 5 symptoms	
Severe: 6 or more symptoms	

Note. Pharmacological treatment is typically indicated for alcohol use disorder of moderate or greater severity and alcohol dependence. APA = American Psychiatric Association; WHO = World Health Organization.

Rationale for the Pharmacological Treatment of Alcohol Use Disorder

Cost-benefit studies of AUD treatment (1967-1997) have consistently found that individuals with untreated AUD utilize health care, and incur medical costs, at a rate about twice that of their age and gender cohorts who are treated for AUD (Holder 1998). Conversely, total health care costs decrease following initiation of treatment for AUD. The combination of FDA-approved medication for AUD and evidence-based behavioral therapy was found to be associated with fewer inpatient admissions and 30% lower total health care costs compared with costs of individuals not receiving medication-assisted treatment (Baser *et al.* 2011). These statistics make a compelling case for considering FDA-approved medications for all patients with AUD. Yet despite these evidence-based findings for efficacy, results from a 2019 nationally representative survey found that fewer than 3% of Americans with past-year AUD were treated with one of the medications approved by the FDA to treat AUD (Han *et al.* 2021). Meta-analyses of controlled trials of acamprosate and naltrexone showed effect sizes that were equivalent to those in meta-analyses of controlled trials of widely used antidepressants for treating major depressive episodes (Jonas *et al.* 2014; Maisel *et al.* 2013; Schalkwijk *et al.* 2014). The relative underutilization of existing effective AUD medications may be a function of factors ranging from inadequate training in this domain to the lack of a financial incentive for the pharmaceutical industry to market AUD medications that are available in inexpensive generic formulations.

Appropriate utilization of pharmacological treatment of AUD has been advanced by subspecialty certifications in addiction psychiatry and addiction medicine (Nunes *et al.* 2020) and by the publication of two important guidelines: the first report on alcohol, drugs, and health from the Office of the Surgeon General (U.S. Department of Health and Human Services 2016) and the American Psychiatric Association (APA) *Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder* (American Psychiatric Association 2017). The Surgeon General's report recommends a chronic care management approach to treating AUD that includes evidence-based behavioral and pharmacological treatment; social support services; and clinical monitoring of adverse events, medication adherence, and symptoms of relapse at each follow-up visit. The report further recommends working collaboratively with patients and their social support systems to communicate the risks and benefits of each treatment option relative to the patients' recovery goals, drug costs, and dosing schedules and ensuring that patients comprehend this information.

The APA practice guideline provides evidence-based recommendations that may facilitate appropriate prescribing of existing medications to treat AUD; it also includes recommendations for prescribing two repurposed medications, gabapentin and topiramate, to treat AUD on the basis of an evaluation of the clinical trial literature generated by academic investigators. Including evidence-based repurposed medications in the APA guideline broadens the available options for effectively treating AUD. The guideline recommends that acamprosate or naltrexone be used by individuals with moderate to severe AUD who wish to cut down on or quit drinking, who prefer medication or who have not responded to nonpharmacological treatments, and who have no contraindications to the use of these medications. These recommendations are based on large-scale meta-analyses that found that either acamprosate or naltrexone combined with counseling showed superior efficacy in increasing rates of abstinence (acamprosate, number needed to treat [NNT] = 2) or no heavy drinking (naltrexone, NNT = 12) relative to placebo administered in conjunction with counseling (Jonas *et al.* 2014). "NNT = 12" indicates that about 12 people would need to be treated to achieve a single case of no drinking or no heavy drinking. No significant difference was found between acamprosate and naltrexone for a return to any drinking or heavy drinking in meta-analyses of those trials that compared acamprosate and naltrexone (Jonas *et al.* 2014). The APA practice guideline further suggests that disulfiram

not be selected as an initial treatment for AUD, given the physiological consequences of combining this medication with alcohol. In addition, this guideline recommends that antidepressant medications not be used for the treatment of AUD, unless there is a co-occurring disorder for which these treatments are indicated. Furthermore, it is noted that the medications approved to treat AUD are not treatments for alcohol withdrawal and should be initiated only following detoxification and/or after abstinence has been established.

Pharmacological Treatment of Alcohol Withdrawal

For some individuals, pharmacological management of alcohol withdrawal symptoms may be required before pharmacological treatment of AUD can be initiated. One of the DSM-5 criteria for AUD is the emergence of acute alcohol withdrawal, with symptoms occurring within several hours to a few days of marked reduction in or abrupt cessation of alcohol intake in individuals with extended periods of heavy drinking. The DSM-5 criteria for alcohol withdrawal are met when two or more of the following eight symptoms are present and cannot be better explained by another disorder, including withdrawal from another substance: 1) autonomic hyperactivity (i.e., a pulse rate greater than 100 bpm), 2) increased hand tremor, 3) insomnia, 4) nausea or vomiting, 5) transient hallucinations, 6) psychomotor agitation, 7) anxiety, and 8) generalized tonic-clonic seizures. The Clinical Institute Withdrawal Assessment for Alcohol--Revised is a widely used scale developed to repeatedly measure the severity of these symptoms over the time course of withdrawal, with a cutoff score greater than or equal to 10 indicating withdrawal symptoms that may require medical intervention (Sullivan *et al.* 1989). Symptoms may last 4-5 days and peak within 2 days of the last drink, reflecting the relatively fast metabolism of alcohol (American Psychiatric Association 2013). If symptoms have not emerged within 2 days of the last drink or are consistently scored less than 10 on the Clinical Institute Withdrawal Assessment for Alcohol--Revised in individuals without a history of alcohol withdrawal seizures or delirium tremens, symptoms can typically be managed without medication (Holt and Tetrault 2022; Sullivan *et al.* 1989). For detailed guidance on managing alcohol withdrawal, including sample medication regimens, readers are referred to *The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management* (American Society of Addiction Medicine 2020).

It is estimated that up to 10% of patients with very heavy alcohol use (e.g., > 8 drinks per day over multiple days) may develop severe withdrawal symptoms that can be life threatening and may include tonic-clonic seizures and delirium tremens (American Psychiatric Association 2013; Hoffman and Weinhouse 2022). Risk for severe withdrawal increases with age, family history or prior history of withdrawal, use of sedative-hypnotic drugs, and concurrent serious medical conditions. Inpatient treatment and close monitoring is typically warranted to mitigate the risk for severe withdrawal. Patients at risk for severe withdrawal, or those who have serious medical conditions that could increase their risk, may be given a front-loading high initial dose of benzodiazepines to prevent symptom onset or to achieve more rapid control of symptoms (Sellers *et al.* 1983). Supportive care includes correction of electrolyte imbalances and nutritional deficiencies.

Outpatient treatment can be considered for pharmacological management of patients not at risk for severe withdrawal who are cognitively intact, able to avoid alcohol and take oral medication, and willing to commit to frequent monitoring (Hayashida *et al.* 1989). Outpatient treatment can be given on a fixed tapering schedule or on a symptom-triggered dosing schedule (Hoffman and Weinhouse 2022; Saitz *et al.* 1994). A significant other can be recruited to monitor withdrawal symptoms and assist the patient in determining when a dose is indicated if symptom-targeted dosing is used. Worsening symptoms, medication misuse, or alcohol use should prompt a higher level of care. All detoxifying patients should be prescribed a multivitamin containing folate and thiamine (see also "Initiation and Monitoring of Pharmacological Treatment" section later in chapter).

Benzodiazepines are the gold standard for treating mild to moderate withdrawal symptoms (e.g., a Clinical Institute Withdrawal Assessment for Alcohol--Revised score > 10 and < 20) and preventing progression to severe alcohol withdrawal (e.g., a Clinical Institute Withdrawal Assessment for Alcohol--Revised score > 20), given their documented effectiveness and high margin of safety (Department of Veterans Affairs and Department of Defense 2021). A Cochrane Review did not find meaningful differences between individual benzodiazepines in terms of safety or efficacy for treating alcohol withdrawal (Amato *et al.* 2010). Longer-acting benzodiazepines (e.g., chlordiazepoxide) lessen the likelihood of breakthrough symptoms. Shorter-acting benzodiazepines (e.g., lorazepam or oxazepam) have fewer metabolites that depend on liver function, which reduces risk in patients with impaired hepatic function or cognitive function. Benzodiazepines are subject to misuse and should not be prescribed beyond the acute withdrawal period. Rather, patients should be engaged in a treatment plan that includes evidence-based behavioral and pharmacological treatment of AUD.

Although benzodiazepines are considered the drugs of choice for treating alcohol withdrawal, anticonvulsants have been studied as an alternative or adjunctive treatment for mild to moderate alcohol withdrawal for patients in whom the risks of benzodiazepines may outweigh benefits (e.g., those who may not have adequate monitoring available or those with abuse liability). For example, gabapentin has some advantages relative to benzodiazepines: it does not interact with alcohol, is less associated with impaired cognition or motor coordination, is not metabolized in the liver, and has low lethality in overdose (Ahmed *et al.* 2019; Mason *et al.* 2018; Myrick *et al.* 2009). These features are attractive, as alcohol detoxification is increasingly provided on an outpatient basis. Of note, comprehensive reviews have concluded that anticonvulsants should not be considered a stand-alone treatment for severe alcohol withdrawal because of their ineffectiveness in suppressing seizures related to alcohol withdrawal (Hammond *et al.* 2015; Leung *et al.* 2015). Initiating gabapentin dosage titration in conjunction with alcohol detoxification may also assist in decreasing withdrawal-related anxiety and insomnia as well as serve as a transition to longer-term relapse prevention treatment (Mason *et al.* 2018; Myrick *et al.* 2009).

FDA-Approved Medications for the Treatment of Alcohol Use Disorder

Three medications are approved by the FDA for the treatment of AUD: disulfiram (Antabuse and generic, oral), naltrexone (ReVia and generic, oral; and Vivitrol, long-acting injectable),

and acamprosate (Campral and generic, oral). Each drug has a different mechanism of action that can be understood within the cyclical framework of AUD, as illustrated in Figure 55-3.

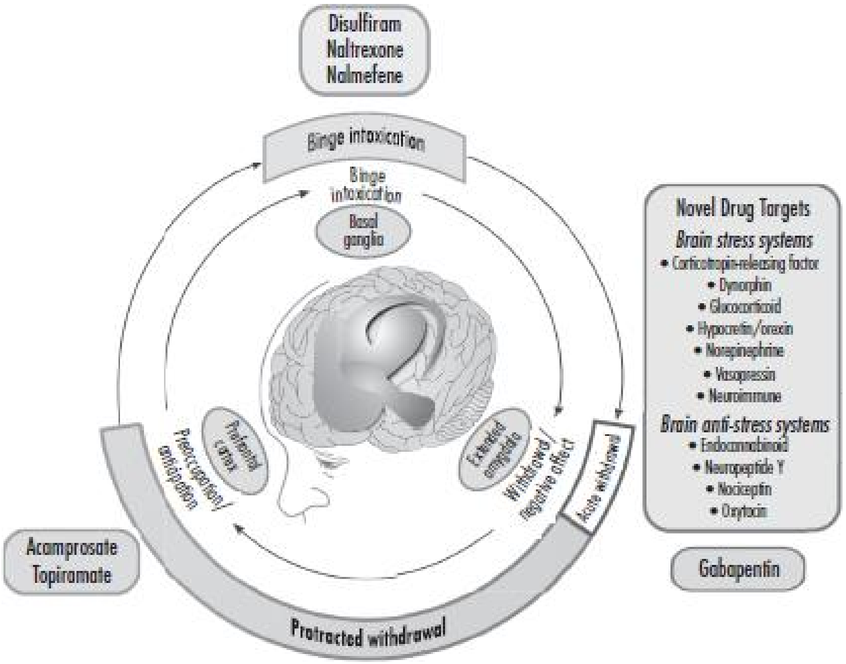
Disulfiram
Naltrexone
Nalmefene
Binge intoxication
Binge intoxication
Basal ganglia
Novel Drug Targets
Brain stress systems
• Corticotropin-releasing factor
• Dynorphin
• Glucocorticoid
• Hypocretin/orexin
• Norepinephrine
• Vasopressin
• Neuroimmune
Brain anti-stress systems
• Endocannabinoid
• Neuropeptide Y
• Nociceptin
• Oxytocin
Gabapentin
Acute withdrawal
Extended amygdala
Withdrawal/negative affect
Prefrontal cortex
Preoccupation/anticipation
Acamprosate
Topiramate
Protracted withdrawal

FIGURE 55-3. Conceptual framework for the effects of various medications on the three major stages of the alcohol addiction cycle and the clinical stages of alcohol use disorder (AUD).

The *outer ring* depicts the clinical stages of AUD. The *inner ring* depicts the three stages of the addiction cycle.

Source. Adapted from Koob GF, Volkow ND: "Neurocircuitry of addiction." *Neuropsychopharmacology* 35(1):217-238, 2010. Copyright (c) 2010, Springer Nature. Used with permission.

Acute (up to 5 days' duration) withdrawal syndrome may emerge upon a marked reduction in or abrupt cessation of drinking and is typically followed by a protracted withdrawal phase of indeterminate duration, with a high risk of relapse to pathological drinking; the clinical phases of AUD are illustrated in the outer ring in Figure 55-3. The negative affect stage of protracted withdrawal includes symptoms of anxiety, dysphoria, and irritability (Geller 1991) and is associated with the activation of brain stress systems, in particular overexpression of corticotropin-releasing factor in the extended amygdala (Koob 2008). Such neuroadaptations extend into the preoccupation-anticipation stage of the addiction cycle (the inner ring in Figure 55-3). Dysregulation in the prefrontal cortex during the preoccupation-anticipation stage drives symptoms of craving and perpetuates residual negative emotional states and sleep disturbance. All these symptoms of protracted withdrawal have been identified as risk factors for drinking relapse (Brower *et al.* 1998; Clark *et al.* 1998; Foster and Peters 1999; Gillin *et al.* 1994; Lowman et al. 1996), and the underlying neurobiology offers a multitude of potential drug targets, as shown in Figure 55-3.

Early FDA-approved medications for AUD targeted the binge/intoxication stage by serving as either a psychological deterrent (disulfiram) or an antagonist of the reinforcing effects of alcohol (naltrexone). Acamprosate, a medication discussed later, supports abstinence through the modulation of activity in the glutamatergic system that is associated with craving and the preoccupation-anticipation stage of protracted withdrawal. Acamprosate tends to have a more benign side-effect profile and to be better tolerated than earlier medications (Mason and Heyser 2010) (Table 55-2). To date, there are no FDA-approved drugs associated with the withdrawal/negative affect stage of the addiction cycle, but repurposed drugs have been identified (e.g., gabapentin), and novel drug targets specific to this stage are under investigation and are discussed later in this chapter.

TABLE 55-2. Summary of FDA-approved medications for the treatment of alcohol use disorder

	Disulfiram (oral)	Naltrexone (oral)	Naltrexone (injectable)	Acamprosate (oral)

	Disulfiram (oral)	**Naltrexone (oral)**	**Naltrexone (injectable)**	**Acamprosate (oral)**
Primary evidence-based outcome	No drinking	No heavy drinking days	Number of heavy drinking days	No drinking
	Double-blind trials, NS [c]	NNT = 12 [d]	WMD = -4.6% [d]	NNT = 12 [d]
	Open-label trials, moderate effect size [c]	NNT = 8.6 [e]		NNT = 7.5 [e]
	Supervised administration trials, large effect size [c]			
Median trial duration	6.5 months [c]	3 months[d]	6 months[f]	6 months[d]
Standard dosing	500 mg/day weeks 1-2; 250 mg/day thereafter	One 50-mg tablet daily	One 380-mg injection monthly	Two 333-mg tablets tid
Cost per month [a]	$50	$32	$1,464	$76
Abstinence baseline	[?] 12 hours (mandatory) [b]	~ 4 days[e]	~ 7 days [b, f]	~ 6 days [e]
Medical contraindications [b]	Use of metronidazole, paraldehyde	Opioid dependence,	Opioid dependence, withdrawal, or use	Severe renal impairment (creatinin

	Disulfiram (oral)	**Naltrexone (oral)**	**Naltrexone (injectable)**	**Acamprosate (oral)**
	, alcohol-containing preparations Severe myocardial disease or coronary occlusion Psychosis	withdrawal, or use Acute hepatitis or liver failure	within 7-10 days Acute hepatitis or liver failure	e clearance [?] 30 mL/min)
Adverse events[b]	Neuritis, neuropathy, hepatitis, hepatic failure, psychosis, drowsiness, fatigue, impotence, headache, acne, allergic dermatitis, metallic/garlic aftertaste	Nausea, headache, dizziness, nervousness, fatigue, insomnia, vomiting, anxiety, somnolence, hepatic injury, hepatitis	[?] 5% and 2x placebo: vomiting, nausea, injection site reactions, muscle cramps, dizziness, syncope, somnolence, sedation, decreased appetite	[?] 3% and > placebo: diarrhea, flatulence, nausea, pain, pruritus

Note. Review each drug's package insert for full prescribing information. NNT = a statistical estimate of the number needed to treat to achieve the specified outcome in one individual; NS = not significantly different from placebo; WMD = weighted mean difference.

[a] Monthly cost estimates were provided by CVS Pharmacy and are based on generic formulations when available.

[b] Information derived from FDA-approved labels.

[c] Skinner *et al.* 2014.

[d] Jonas *et al.* 2014.

[e] Maisel *et al.* 2013.

[f] Garbutt *et al.* 2005.

Disulfiram

Disulfiram was the first FDA-approved (in 1951) pharmacotherapy for AUD. It inhibits the enzyme aldehyde dehydrogenase, so that if even small amounts of alcohol are consumed, acetaldehyde quickly builds up, with rapid onset of a disulfiram-alcohol interaction that includes flushing, nausea and vomiting, changes in mental status, and multiple cardiac and respiratory symptoms that could be fatal in severe reactions. Disulfiram thus is used as a deterrent to alcohol use and should never be given to patients when in a state of alcohol intoxication or without their full knowledge. The psychological threat of the disulfiram-alcohol interaction, as opposed to the drug's pharmacodynamic properties, may be the primary mechanism of disulfiram's deterrent effect (Skinner *et al.* 2014). The fear of a disulfiram-alcohol interaction is equivalent across groups in placebo-controlled double-blind trials and mitigates against detecting disulfiram treatment effects relative to placebo. A meta-analysis of randomized open-label trials found a moderate effect of disulfiram relative to various comparison groups; the effect of disulfiram was found to be large under conditions of supervised administration (Skinner *et al.* 2014). Disulfiram tablets are taken orally each morning, starting with 500 mg/day for the first 1-2 weeks, then decreasing to 250 mg each morning thereafter. Medication adherence is a demonstrated problem with disulfiram (Fuller *et al.* 1986), and outcomes are optimized with supervised administration (e.g., by a spouse or roommate) in compliant patients (Jorgensen *et al.* 2011). Supervised administration may also be achieved via a Zoom check-in, and a Bluetooth-enabled smart pill dispenser can be used that sends notifications to avoid missed doses.

Disulfiram may be considered for patients with a clear goal of complete abstinence, who are capable of understanding the risks of an alcohol-disulfiram interaction, who have no medical contraindications, and who prefer disulfiram or have not responded to acamprosate and naltrexone (American Psychiatric Association 2017). Prior to initiating treatment with disulfiram, patients should receive a physical exam with electrocardiogram and liver function tests (LFTs). Disulfiram is medically contraindicated in patients who have had a recent myocardial infarction or coronary artery disease, or have a history of a seizure disorder, or are psychotic. It should be used with caution and enhanced monitoring in patients with a history of psychosis, as psychotic reactions have been noted. Metronidazole, paraldehyde, and alcohol-containing preparations like sertraline oral concentrate and cough syrups are contraindicated, as are alcohol-containing mouthwash, hand sanitizers, aftershaves, sauces, salad dressings, and desserts and any other food preparation that might include alcohol to avoid precipitating an alcohol-disulfiram interaction. The intensity of the interaction varies across individuals but is generally proportional to the amounts of disulfiram and alcohol ingested. The duration of the reaction ranges from 30 to 60 minutes to several hours, or as long as there is alcohol in the blood. Patients should be instructed to abstain from alcohol for at least 12 hours and have a zero BAC before taking disulfiram. They should also be advised that reactions with alcohol can occur up to 14 days after taking disulfiram.

Repeat LFTs should be obtained periodically, as elevations in hepatic enzymes--and, more rarely, potentially fatal acute hepatotoxicity--commonly occur even after months of treatment and in patients with normal baseline liver function (National Institute of Diabetes and Digestive and Kidney Diseases 2021). Patients should be instructed to seek immediate medical attention if signs and symptoms of liver toxicity occur (fatigue, weakness, persistent abdominal pain, nausea, vomiting, jaundice, or dark urine). It is suggested that patients carry a wallet card noting that they are taking disulfiram in case of medical emergency.

A meta-analysis found more serious adverse events with disulfiram than with comparison treatments (Skinner *et al.* 2014). The alcohol-disulfiram interaction has inherent risks, which some patients use to strengthen their motivation to abstain from alcohol. Many have found disulfiram to be well tolerated when taken as prescribed (Chick 1999). The potential benefit of disulfiram for appropriately selected patients who prefer this treatment has been found to outweigh the harms, in particular given the risks of continued alcohol misuse (American Psychiatric Association 2017).

Naltrexone

Naltrexone is a pure opioid receptor antagonist that was originally approved by the FDA as a treatment for opioid dependence in 1984. It was repurposed and approved by the FDA 10 years later for the treatment of alcohol dependence (oral, 1994; long-acting injectable, 2006). Opioid receptor antagonism as a treatment strategy for AUD is based on the hypothesis that if alcohol consumption is less rewarding, drinking will decrease. A reduction in the rate of heavy drinking is the positive outcome most commonly reported in clinical trials of naltrexone for the treatment of AUD (Jonas *et al.* 2014; Maisel *et al.* 2013). Problems with medication nonadherence have been noted with oral naltrexone (Volpicelli *et al.* 1997), and thus a long-acting (30-day) injectable formulation was developed. A systematic review and meta-analysis included 53 randomized controlled trials of oral naltrexone (50 mg/day) for the treatment of AUD (Jonas *et al.* 2014). The included studies involved 9,140 patients and treatment durations of 12 weeks or longer. Naltrexone was found to significantly decrease the likelihood of a return to heavy drinking (NNT = 12) and, to a lesser extent, a return to any drinking (NNT = 20). This finding replicates results from an earlier meta-analysis that found an NNT of 8.6 for a reduction in heavy drinking associated with naltrexone (Maisel *et al.* 2013). This earlier meta-analysis also assessed clinical moderators of the response to naltrexone treatment and found that about 4 days of abstinence prior to beginning treatment significantly improved the treatment response. In addition, treatment goals other than abstinence were associated with a larger effect size for reducing heavy drinking than the goal of complete abstinence. Studies of potential genetic moderators of naltrexone response have focused on m opioid receptor gene polymorphism status. Initial enthusiasm for this pharmacogenetic approach was based on secondary analyses of completed clinical trials that found patients might be more responsive if they have at least one G allele of the A118G polymorphism of *OPRM1* (Anton *et al.* 2008b; Kranzler *et al.* 2013; Oslin *et al.* 2003). However, subsequent studies found no association between genotype and naltrexone response, including a negative clinical trial that prospectively stratified patients on the basis of their *OPRM1* genotype (Oslin *et al.* 2015). A review concluded that these conflicting results do not support a role for *OPRM1* genotype determination in clinical practice (Jones *et al.* 2015).

There have been no head-to-head comparisons of the efficacy of oral versus injectable naltrexone to date. A meta-analysis of drinking outcomes among 1,926 participants in two trials examining different formulations of injectable naltrexone found no significant effects of treatment on time to return to any drinking or heavy drinking, but did find a reduction in the number of heavy drinking days (weighted mean difference [WMD], -4.6%). The trials, conducted in support of FDA approval, found a similar reduction in heavy drinking days with Vivitrol 380 mg/month, but only for men and those with 7 days of abstinence prior to randomization (Garbutt *et al.* 2005).

Any form of naltrexone treatment for AUD is contraindicated in patients who are physiologically dependent on opioids, who are in opioid withdrawal, who have used prescribed or illicit forms of opioids within 7-10 days, or who have findings on a urine drug screen (UDS) positive for opioids. The reason for these prohibitions is to avoid unintended precipitation of opioid withdrawal through the administration of an opioid antagonist. Naltrexone has the capacity to cause hepatocellular injury when used in higher than recommended dosages and is contraindicated in patients with acute hepatitis or liver failure. Naltrexone has not been evaluated in patients with severe hepatic impairment, and clinical trials of naltrexone tend to exclude patients with LFT values greater than three times the upper limit of normal. Caution is also advised when using naltrexone to treat patients with moderate to severe renal impairment because naltrexone and its primary metabolite are excreted primarily in the urine, and it has not been studied in patients with moderate or greater renal impairment.

To manage risk, baseline medical screening for naltrexone treatment may include tests of renal and hepatic function and a UDS. Repeat LFTs (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyltransferase [GGT]) may verify the absence of naltrexone-related hepatic enzyme abnormalities. Patients may be advised to carry a wallet card indicating they are receiving naltrexone. In the case of an emergency requiring pain management, nonopioid analgesics or regional analgesia can be used. Naltrexone will also antagonize the effects of opioid-based remedies (e.g., for coughs or diarrhea), so nonopioid-based treatments should be selected. A meta-analysis found a higher risk for discontinuation due to adverse events with naltrexone relative to placebo; common side effects included nausea, vomiting, and dizziness (Jonas *et al.* 2014). Patients receiving Vivitrol may also experience a range of injection site reactions. Patients should be advised not to drive or operate heavy machinery until they are comfortable with how the drug affects them. They should also be advised to seek medical attention if they experience symptoms of acute hepatitis (persistent stomach pain, dark urine, tiredness, yellowing of the whites of the eyes).

The majority of clinical trials of naltrexone have been 3 months in duration. Two early studies found that treatment effects were no longer significant relative to placebo 1 to 3 months after treatment (Anton *et al.* 2001; O'Malley *et al.* 1996). Given that the antagonist effect of the drug does not persist beyond drug elimination, pairing naltrexone with a coping skills/relapse prevention form of cognitive-behavioral therapy (CBT) may offer an optimal treatment strategy whereby heavy drinking is tempered pharmaceutically and behavioral therapy facilitates the lifestyle characteristic of long-term recovery (O'Malley *et al.* 1992).

Acamprosate

Acamprosate was developed in France in the 1980s and was approved by the FDA in 2004 for the maintenance of abstinence in detoxified alcohol-dependent individuals. Acamprosate is a synthetic compound with a chemical structure similar to that of GABA and the amino acid neuromodulator taurine. Repeated cycles of heavy drinking and withdrawal dysregulate the balance between neuronal excitation (e.g., glutamatergic) and inhibition (e.g., GABAergic). Glutamatergic hyperactivity is associated with alcohol craving and the preoccupation-anticipation stage of the addiction cycle (see Figure 55-3). A preponderance of the preclinical literature suggests that the salient action of acamprosate in AUD is restoration of homeostasis in *N*-methyl-D-aspartate-mediated glutamatergic neurotransmission in early abstinence (Littleton 2007). In contrast to disulfiram, which induces aversion through negative physical effects, or naltrexone, which tempers the pleasurable effects of alcohol, acamprosate acts to normalize the dysregulation in neurochemical systems that has been implicated in the biological mechanisms of AUD. Consistent with this hypothesis, a pharmacometabolomics study identified elevated baseline serum glutamate as a biomarker of acamprosate response in 120 alcohol-dependent patients. Baseline serum glutamate levels were found to be significantly higher in responders compared with nonresponders, and serum glutamate levels of responders were normalized after acamprosate treatment, whereas there was no significant change in glutamate in nonresponders (Nam *et al.* 2015). These results suggest that elevated baseline serum glutamate levels may be a potential biomarker associated with positive acamprosate response. Developing and validating such predictors may improve patient treatment matching and optimize treatment efficacy.

Acamprosate requires around a week to reach steady-state levels in the nervous system. The majority of acamprosate clinical trials are 6-12 months in duration (see Table 55-2). A limited number of posttreatment follow-up studies have shown the effects of acamprosate to be sustained for periods up to 1 year after the last dose, consistent with its action in restoring and maintaining homeostasis in brain glutamate activity (Mason and Heyser 2010). Meta-analyses of 27 acamprosate randomized controlled trials involving 7,519 adults with AUD found that the NNT to prevent a return to any drinking with acamprosate was 12 (Jonas *et al.* 2014). These findings corroborate results from a meta-analysis reporting an NNT of 7.5 for attainment of complete abstinence; detoxification and required abstinence (mean = 6.2 +- 5.5 days) prior to acamprosate administration were associated with increased efficacy (Maisel *et al.* 2013).

Similarly, a multicenter trial conducted in the United States found patient choice of abstinence as a treatment goal to be predictive of acamprosate efficacy (Mason *et al.* 2006). Another meta-analysis that obtained individual records from 1,317 women and 4,794 men who participated in 22 acamprosate studies found an incremental gain of 10.4% ($P < 0.001$) in the percentage of abstinent days, an incremental gain of 11.0% ($P < 0.001$) in the percentage of no heavy drinking days, an OR of 1.9 ($P < 0.001$) for rate of complete abstinence, and an OR of 1.9 ($P < 0.001$) for rate of no heavy drinking over the study duration, with no differences in the rate of discontinuation due to adverse events or severity or type of adverse event for patients treated with acamprosate relative to placebo (Mason and Lehert 2012). Acamprosate was also associated with significantly higher rates of treatment completion ($P = 0.004$) and medication compliance ($P < 0.001$) than placebo.

Acamprosate has low bioavailability, which requires that divided doses (two 333-mg tablets) be taken three times daily. It is suggested that patients set reminders on their smartphones, place a 1-week supply of acamprosate in a pill tray (purchased over the counter [OTC]) with the day and time of dose indicated, or use a Bluetooth-enabled smart pill dispenser that sends notifications to avoid missed doses. Acamprosate is excreted primarily by the kidneys. Given the risk of accumulation of acamprosate with prolonged administration of therapeutic doses in patients with renal impairment (Wilde and Wagstaff 1997), the use of acamprosate is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min); a dosage adjustment to one 333-mg tablet administered three times daily is recommended for patients with moderate renal impairment (creatinine clearance 30-50 mL/min; Saivin *et al.* 1998; Wilde and Wagstaff 1997). No dosage adjustment is required for patients with mild renal impairment (creatinine clearance > 50 mL/min). Acamprosate is not metabolized by the liver and can be given safely to patients with liver disease. It is not associated with drug-drug interactions. It does not interact with alcohol (as does disulfiram), nor does it precipitate opioid withdrawal in patients using opioids (as does naltrexone). Acamprosate has also been found to not interact with medications commonly prescribed to individuals with AUD, such as disulfiram, antidepressants, anxiolytics, or hypnotics (Rosenthal *et al.* 2008). Pharmacokinetic studies found that coadministration with naltrexone increased the rate and extent of acamprosate absorption without compromising tolerability (Johnson *et al.* 2003; Mason *et al.* 2002). These results suggest that this combination therapy may improve acamprosate's bioavailability. Diarrhea, typically mild to moderate at the start of treatment, is the side effect most commonly associated with acamprosate (17%) relative to placebo (10%) (Merck Sante 2005). Adverse events of a suicidal nature were infrequent in clinical trials but were more frequent with acamprosate than placebo treatment (1.4% vs. 0.5% in studies of 6 months' duration or less, 2.4% vs. 0.8% in year-long studies). Patients should be monitored for the emergence of symptoms of depression or suicidality. Meta-analyses found acamprosate to be not significantly different from placebo in terms of risk of withdrawal from treatment due to adverse events (Jonas *et al.* 2014; Mason and Lehert 2012).

Summary

In summary, acamprosate, naltrexone, and disulfiram are evidence-based FDA-approved pharmacotherapies for AUD that have been used safely and effectively for

decades. The potential benefits for appropriately selected patients have been found to outweigh the harms, in particular given the risks of continued alcohol misuse (American Psychiatric Association 2017). A comparative summary of treatment parameters for these medications is presented in Table 55-2. Each variable in Table 55-2 is derived from the most comprehensive data available, including meta-analyses, package inserts, and multicenter trials.

APA Practice Guideline Recommendations for Medications Repurposed for Treatment of Alcohol Use Disorder

The underutilization of existing pharmacotherapies points to a need for new medications to safely and effectively treat AUD. Repurposing existing medications with known safety and tolerability profiles that are FDA approved for other indications may help to expeditiously meet this need. Topiramate and gabapentin, two drugs that were originally developed as antiepileptic medications, have shown therapeutic potential for AUD in multiple investigator-initiated trials. The APA practice guideline recommends that topiramate or gabapentin be offered to patients who have a goal of decreasing or quitting drinking, who prefer these medications to the other available options, or who cannot tolerate or have not responded to acamprosate and naltrexone and have no contraindications to the use of these medications (American Psychiatric Association 2017). Co-occurring disorders, concomitant medications, and side-effect profiles are additional factors that may guide the selection of topiramate or gabapentin. Antiepileptic drugs, including gabapentin and topiramate, increase the risk of suicidal thoughts or behavior in about 1 in 500 patients who take these drugs for any indication. An assessment of suicidality at baseline and throughout treatment is therefore warranted. In addition, abrupt withdrawal from these drugs has precipitated seizures and status epilepticus; thus, on-and-off titration is indicated.

Topiramate

Topiramate (Topamax and generic) was approved by the FDA as an oral antiepileptic drug in 1998 and for prophylaxis of migraine in 2004. Topiramate is hypothesized to act in AUD by reducing alcohol's reinforcing effects by facilitating GABAergic function and inhibiting glutamatergic pathways in the corticomesolimbic system (Johnson *et al.* 2007). A meta-analysis of randomized controlled trials of 3 months' duration with dosage titration to a target dosage of 200-300 mg/day found topiramate to be associated with fewer drinking days (WMD, -6.5%), fewer heavy drinking days (WMD, -9%), and fewer drinks per drinking day (WMD -1.0) than placebo (Jonas *et al.* 2014). Of note, patients were typically not required to be abstinent at the start of treatment, although concomitant behavioral therapy was provided that was oriented to working toward abstinence or nonharmful drinking. A pharmacogenetic study found topiramate's effect on heavy drinking to be moderated by rs2832407, a noncoding single nucleotide polymorphism in *GRIK1*, which suggests a role for the kainate receptor in the mechanism of topiramate's effect on heavy drinking (Kranzler *et al.* 2014). If the effect is replicated, this genetic marker may identify patients likely to respond to topiramate.

Topiramate has no contraindications but has a number of warnings and precautions. To mitigate risk, recommended lab tests include baseline and periodic measures of serum bicarbonate to detect treatment-emergent metabolic acidosis, baseline tests of renal function because creatinine clearance greater than 70 mL/min requires a dosage adjustment to half the usual starting and maintenance dosage, and baseline tests of hepatic function because topiramate plasma concentration is increased in hepatic impairment.

Meta-analyses found that patients with AUD who were treated with topiramate had a higher risk of cognitive dysfunction (number needed to harm [NNH] = 12), paresthesias (NNH = 4), and taste abnormalities (NNH = 7) than did patients treated with placebo (Jonas *et al.* 2014). Cognitive dysfunction is an adverse event commonly associated with topiramate, symptoms of which may include confusion; psychomotor slowing; attention, concentration, and memory impairment; and speech or language problems (in particular, word-finding difficulties [Salinsky *et al.* 2005]). Other adverse events involving the CNS include dizziness, somnolence, fatigue, depression, and mood problems. CNS events are often dosage related and more likely to occur with a rapid dosage titration and high initial dosage. Other warnings include risk for acute myopia and secondary angle closure glaucoma, decreased sweating and increased body temperature, suicidal behavior and ideation, kidney stones, hyperammonemia, and encephalopathy. Patients with and without a history of seizure should be gradually withdrawn from topiramate to minimize the potential for seizures. Topiramate interacts pharmacokinetically with some antiepileptic drugs, CNS depressants, oral contraceptives, metformin, lithium, and carbonic anhydrase inhibitors, with significant changes in drug plasma concentrations; refer to the package insert for guidance. Topiramate is Category D in pregnancy. Exposure to topiramate in utero increases the risk of cleft lip and/or palate, in particular if exposure occurs in the first trimester (when many women do not know they are pregnant). Topiramate passes into breast milk.

Gabapentin

Gabapentin (Neurontin and generic) was approved by the FDA as an oral antiepileptic drug in 1993 and as a treatment for postherpetic neuralgia in 2002. A once-daily extended-release formulation (Gralise) and a gabapentin prodrug (Horizant) are FDA approved for postherpetic neuralgia, and

Horizant is approved for restless legs syndrome. All but one trial in AUD were conducted with the original gabapentin formulation.

Gabapentin is an amino acid designed as a structural analogue of GABA and is not a direct GABA agonist (Sills 2006). Gabapentin binds to the alpha-2-delta type 1 subunit of voltage-gated calcium channels (Uchitel *et al.* 2010; Xiao *et al.* 2007). Gabapentin selectively inhibits Ca^{2+} influx through these voltage-operated Ca^{2+} channels (Fink *et al.* 2000), which results in its ability to reduce postsynaptic excitability and decrease the release of excitatory neurotransmitters (Cunningham *et al.* 2004). Possibly via its actions to block excitatory neurotransmission, gabapentin increases the concentration of GABA in the brain (Gotz *et al.* 1993; Taylor *et al.* 1998). In animal models of alcohol dependence, gabapentin decreased amplitudes of GABA receptor-mediated inhibitory postsynaptic currents in the central nucleus of the amygdala and decreased alcohol drinking (Roberto *et al.* 2008). As shown in Figure 55-3, the extended amygdala is the key brain region associated with negative affect in protracted withdrawal.

The potential efficacy of gabapentin as a treatment for AUD was assessed in a human laboratory model of protracted withdrawal. Non-treatment-seeking volunteers with alcohol dependence who were randomly assigned to double-blind treatment with 1,200 mg/day gabapentin showed significantly less craving when exposed to in vivo alcohol cues after 3 days of abstinence and also had improved sleep quality, latency, and efficiency relative to volunteers taking placebo (Mason *et al.* 2009). Support for the safety and efficacy of gabapentin as a treatment for AUD is provided by a number of investigator-initiated single-site treatment studies (Anton *et al.* 2009, 2011, 2020; Brower *et al.* 2008; Chompookham *et al.* 2018; Furieri and Nakamura-Palacios 2007; Karam-Hage and Brower 2000, 2003; Mason *et al.* 2014). Studies have mostly been double-blind, placebo-controlled designs with random assignment and have been conducted across multiple geographic regions, including North and South America and Asia. A systematic review found that studies requiring 3 or more days of abstinence at treatment initiation showed the most robust treatment effects (Mason *et al.* 2018). Conversely, studies that did not require abstinence at treatment initiation or that involved alcohol administration were unlikely to show efficacy for gabapentin for craving and/or drinking outcomes. Studies that evaluated two dosages of gabapentin found greater efficacy for the higher dosage (1,200 mg/day, 1,600 mg/day, or 1,800 mg/day) relative to the lower dosage studied (900 mg/day) (Mason *et al.* 2014; Myrick *et al.* 2009; Salehi *et al.* 2011). A 12-week trial (*N* = 150) of 0 mg/day, 900 mg/day, and 1,800 mg/day gabapentin found significant linear dosage effects on rates of abstinence, rates of no heavy drinking, number of drinks per week, and number of drinking days per week, and on secondary measures of craving, negative affect, and insomnia (Mason *et al.* 2014). The 1,800-mg/day dosage was associated with an NNT of 5 for no heavy drinking and an NNT of 8 for complete abstinence. A multicenter trial of gabapentin enacarbil 1,200 mg/day did not find efficacy for AUD but did include a pharmacokinetic analysis that found higher levels of gabapentin in plasma to be associated with lower alcohol consumption (Falk *et al.* 2019). An independent reanalysis of the clinical data was conducted to identify a profile of likely responders; this subset showed a significantly greater effect of gabapentin enacarbil on the rate of heavy drinking and number of drinks per week relative to placebo (Laska *et al.* 2020).

Studies of FDA-approved indications have often reported a secondary beneficial effect of gabapentin on measures of sleep. Administration of alcohol at bedtime to normally functioning subjects was used to induce sleep disruption in a double-blind, randomized crossover study of gabapentin in a sleep lab setting with polysomnography and subjective measures (Bazil *et al.* 2005). Gabapentin improved sleep by significantly decreasing stage 1 sleep and the number of awakenings and increasing sleep efficiency relative to placebo. Importantly, gabapentin did not differ from placebo on tests of daytime drowsiness or performance. Off-label clinical studies and multiple studies of AUD report beneficial effects of gabapentin on sleep as well as on subsyndromal anxiety and mood symptoms (for a review, see Mason *et al.* 2018). These clinical findings are consistent with basic research suggesting that gabapentin may support recovery by restoring homeostasis in brain stress systems that become dysregulated in the protracted withdrawal/negative affect phase of AUD (Roberto *et al.* 2008). Research suggesting that gabapentin may be most effective in individuals with symptoms of acute alcohol withdrawal was challenged because individuals with clinically significant symptoms of acute alcohol withdrawal were systematically excluded from participation in this research (Anton *et al.* 2020; Kleinman and Ostacher 2020). However, initiating gabapentin dosage titration in conjunction with alcohol detoxification may assist in decreasing withdrawal-related anxiety and insomnia as well as serve as a transition to longer-term relapse prevention treatment during protracted withdrawal (Myrick *et al.* 2009). Gabapentin should not be considered a stand-alone treatment for severe acute alcohol withdrawal because of its ineffectiveness in suppressing seizures related to alcohol withdrawal. The APA practice guideline recommends that gabapentin be used for the treatment of AUD, not alcohol withdrawal.

All gabapentin treatment studies were conducted in patients who concomitantly received behavioral treatment. Systematic reviews and meta-analyses suggest that combining gabapentin with behavioral support provides an incremental advantage in drinking outcomes relative to behavioral support with placebo (Cheng *et al.* 2020; Kranzler *et al.* 2019; Leung *et al.* 2015; Mason *et al.* 2018). Gabapentin may be a useful treatment for patients with AUD and symptoms of sleep disturbance and negative affect, as well as those with chronic pain syndromes, per the FDA-approved pain indication for gabapentin.

There are no contraindications to gabapentin other than known hypersensitivity to the medication. Gabapentin is not metabolized in the liver and can be used safely by patients with liver disease. It is eliminated from systemic circulation by renal excretion as unchanged drug. A baseline test of creatinine clearance is indicated. The dosage should be adjusted for patients with reduced renal function (creatinine clearance < 60 mL/min). Gabapentin ([?] 1,800 mg/day) resulted in no serious safety concerns among the approximately 1,000 outpatients with AUD who participated in studies up to 12 weeks in duration at dosages up to 1,800 mg/day. Adverse events tended to be mild to moderate and tended not to differ from placebo. Common adverse events included headache, insomnia, fatigue, muscle aches, and various gastrointestinal complaints in patients with AUD treated with both gabapentin and placebo (Mason *et al.* 2018). Common side effects with gabapentin enacarbil were fatigue, dizziness, and somnolence (Falk *et al.* 2019). Gabapentin treatment outcomes and adverse effects do not appear to differ between men and women with AUD. On the basis of clinical and postmarketing experience from use for approved pain and epilepsy indications, gabapentin is considered to have a good safety and tolerability profile. The most commonly reported adverse events with gabapentin in comparison with placebo in non-AUD pivotal trials have included dizziness, somnolence, peripheral edema, ataxia, fatigue, and nystagmus. As with any centrally active drug, patients should be advised not to drive motor vehicles or operate heavy machinery until they have ascertained that the drug does not affect their performance. As with other anticonvulsants, monitoring for suicidality and titrating off treatment to reduce seizure risk are indicated.

Reports of abuse of gabapentinoids, such as gabapentin and pregabalin, are increasingly being documented in high-risk populations, notably abusers of opioids and prescription drugs. Alcohol was not found to interact meaningfully with gabapentin in a pharmacokinetic/pharmacodynamic alcohol-gabapentin drug interaction study, nor was gabapentin found to increase BACs or the intoxicating, stimulating, or sedating effects of alcohol (Bisaga and Evans 2006). There was no evidence of tolerance to gabapentin, rebound with titration off the drug, or abuse potential in AUD clinical trials. However, patients who are undergoing opioid withdrawal, those who misuse prescriptions recreationally, and prison populations may be at increased risk of misusing gabapentin, with self-administered doses often far exceeding (by 3-25 times) the therapeutic range (Bastiaens *et al.* 2016; Chiappini and Schifano 2016; Hakkinen *et al.* 2014; Smith *et al.* 2016; Wilens *et al.* 2015). Patients with such risk histories should be monitored for potential gabapentinoid misuse or diversion (e.g., self-escalation of dosage or a "need" for unusually high dosages, repeated requests to replace "lost" medication).

Drugs Approved Outside of the United States for the Treatment of Alcohol Use Disorder

Nalmefene

Nalmefene is an opioid antagonist that is structurally similar to naltrexone but binds more potently to a broader range of opioid receptor subtypes (i.e., the m, d, and k opioid receptors [Michel *et al.* 1985]). Its activity at the k opioid receptor is of interest because activation of this receptor is not associated with alcohol's rewarding effects, as is the case with the m opioid receptor, but instead is linked to increases in anxiety and dysphoria. Consequently, by blocking both the rewarding effects of alcohol and also some of alcohol's anxiogenic and dysphoric effects, nalmefene functions like an opioid partial agonist. Two seminal 12-week double-blind, placebo-controlled clinical trials demonstrating the therapeutic potential of nalmefene (dosages of 10 mg/day, 20 mg/day, 40 mg/day, or 80 mg/day) for the treatment of AUD were conducted in the United States (Mason *et al.* 1994, 1999). Nalmefene at dosages greater than or equal to 20 mg/day was found to significantly reduce the risk of heavy drinking relative to placebo in outpatients with alcohol dependence, with a rapid onset of effects, which were evident at the first weekly clinic visit.

The European Medicines Agency approved nalmefene (trade name Selincro) in 2013 to help reduce alcohol consumption in adults with alcohol dependence who have a high drinking risk level according to World Health Organization (WHO) criteria (men > 60 g/day and women > 40 g/day) that is sustained for 2 weeks after initial assessment, with nalmefene to be taken 2 hours prior to an anticipated heavy drinking situation. The European Medicines Agency stipulated that nalmefene be used in conjunction with counseling and only by individuals who do not have symptoms of physical withdrawal and do not require detoxification. The agency based its approval on data from two 6-month multicenter trials spanning 11 European countries and involving 1,322 men and women with alcohol dependence. Nalmefene was significantly more effective than placebo in reducing the number of heavy drinking days and daily alcohol consumption (Gual *et al.* 2013; Mann *et al.* 2013; van den Brink *et al.* 2014). In addition, a two-level reduction in

WHO drinking risk levels was examined for treatment effects. These risk levels--very high, high, moderate, and low--are defined on the basis of estimated mean daily ethanol consumption in grams and associated harms (World Health Organization 2000). Secondary analyses found that significantly more nalmefene-treated patients had a two-category downward shift in WHO drinking risk levels relative to those treated with placebo and showed associated

improvements in LFT values and in both clinician ratings and self-ratings of mental and physical health (Aubin *et al.* 2015). Analyses of additional datasets have shown that one-and two-level reductions in WHO drinking risk levels are stable for up to 3 years after treatment and are associated with significantly better mental and physical health and quality of life (Witkiewitz *et al.* 2020).

Thus, both the FDA-approved heavy drinking outcomes and the WHO risk level-based outcomes have broad clinical relevance for individuals who recognize that they have a problem with alcohol but are not ready to quit drinking entirely. An indirect meta-analysis compared four placebo-controlled trials of nalmefene and 13 naltrexone trials and found a significant advantage for nalmefene relative to naltrexone in terms of drinking quantity and frequency (Soyka *et al.* 2016). Findings for the efficacy of nalmefene 20 mg/day taken as needed in adults with alcohol dependence at high drinking risk or greater have been replicated in Japan (Higuchi *et al.* 2020; Miyata *et al.* 2019); nalmefene is now approved for use in reduction of alcohol consumption in many countries worldwide but to our knowledge has not been submitted for FDA approval.

Baclofen

Baclofen (Lioresal and generic) is an oral selective $GABA_B$ receptor agonist (for a review, see de Beaurepaire *et al.* 2019). Baclofen was approved by the FDA in 1977 for the treatment of muscle spasticity secondary to neurological conditions. In 2018 the French Medicines Agency granted marketing authorization for baclofen (at a maximum dosage of 80 mg/day) to support drinking reduction in alcohol dependence after other approved drugs have failed. It has been hypothesized that the pharmacotherapeutic action of baclofen in AUD may be to suppress the ventral tegmental area dopamine system and blunt reinforcement. The approval in France was driven by reports of widespread off-label use of baclofen and not based on scientific evidence. Initial reports were positive in 39 male participants with AUD, showing that treatment with baclofen 30 mg/day increased the percentage of individuals who achieved and maintained abstinence and decreased the number of drinks per drinking day and anxiety levels (Addolorato *et al.* 2002). However, these results have not been consistently observed in subsequent studies or in treatment settings using dosages up to 300 mg/day (Minozzi *et al.* 2018). In addition, the use of baclofen remains controversial, in part because of uncertainty regarding dosing and efficacy along with concerns about safety. A pharmacoepidemiological cohort study found a dose-dependent increased mortality risk with baclofen in alcohol dependence (Chaignot *et al.* 2018). Individuals should be informed to avoid drinking while taking the drug, as the sedative properties of both drugs may potentiate each other. Individuals should be advised not to drive motor vehicles or operate heavy machinery until they have ascertained that the drug does not affect their performance. Individuals should also be advised of the risk of overdose. Side effects range from moderate to more dangerous and include seizures, respiratory depression with sleep apnea and potentially coma (in case of intoxication), severe mood disorders (mania or depression, with the risk of suicide), exacerbation of psychosis, and mental confusion/delirium. Baclofen is mostly (~ 80%) eliminated from systemic circulation by renal excretion as unchanged drug. Therefore, baseline and repeated tests of renal function are recommended given that renal problems can lead to an accumulation of baclofen that may result in mental confusion.

Baclofen treatment should start and end gradually, as there is a withdrawal syndrome associated with abrupt cessation of treatment; withdrawal symptoms may include confusion, agitation, seizures, and delirium and may be confused with alcohol withdrawal (Rolland *et al.* 2014). A consensus statement by a panel of international experts on the use of baclofen for AUD concluded that more research is needed to clarify the potential efficacy and safety of baclofen in treating AUD (Agabio *et al.* 2018).

Initiation and Monitoring of Pharmacological Treatment

A baseline of alcohol use should be established, preferably using quantitative self-report and biochemical measures, against which treatment effects can be tracked. Likewise, harmful effects of alcohol on the patient's health, functioning, and legal status should be documented. The clinician should rule out concomitant disorders such as nicotine and other substance use disorders (SUDs), which may influence AUD outcome if left untreated. Risk of suicide may be elevated in patients with AUD; although rare, suicide has occurred in patients taking pharmacotherapies for AUD. Therefore, screening for suicidality at baseline and periodically thereafter may identify an increased suicide risk that requires further intervention. An integrated treatment plan specific to the patient should be developed to address both AUD and clinically significant concurrent conditions.

Patient safety is optimized by adhering to the recommended dosage and noting the medical contraindications and cautions on the product label. A physical exam and laboratory testing are recommended before treatment is initiated and may help with subsequent monitoring of response to treatment (Center for Substance Abuse Treatment 2009). Useful tests include an alcohol breathalyzer reading, a UDS, LFTs (ALT, AST, GGT), bilirubin, compete blood count, testing for vitamin deficiencies, renal function tests (a standard panel for urea [blood urea nitrogen], electrolytes, and serum creatinine), and a pregnancy test for women of childbearing potential. Obtaining a baseline UDS, LFTs, and measures of creatinine clearance may guide medication selection. A UDS may provide information about otherwise undisclosed drug use, including opioid use, which is exclusionary for naltrexone treatment of AUD. Baseline LFTs may detect clinically significant hepatic impairment that would rule out treatment with disulfiram and naltrexone. Similarly, a baseline test of creatinine clearance may identify severe impairment (< 30 mL/min) in creatinine clearance that would contraindicate the choice of acamprosate. It is recommended that individuals taking disulfiram have repeat bilirubin and LFTs at 2 weeks, then monthly for 6 months and every 3 months thereafter. Carrying a wallet card is advisable to notify emergency personnel that the patient is taking naltrexone (e.g., should anesthesia or pain management be required) or disulfiram (e.g., in case an alcohol-disulfiram interaction is precipitated).

The patient should be informed about what to expect from taking a medication: how it may help AUD and potential risks and side effects. A patient information sheet providing this information in writing can be taken home by the patient for future reference.

A phone call can be scheduled with the patient for a few days after a prescription has been provided to facilitate successful initiation of medication, address any concerns, and assess medication adherence and side effects. Given the common side effects of drowsiness and dizziness, patients should be advised at baseline to avoid driving a car or operating heavy machinery until they are reasonably certain that the drug does not affect their ability to engage in such activities. OTC remedies (e.g., Pepto-Bismol) may be used, if needed, for diarrhea and nausea. Patients should be given a phone number to call and instructed to inform their treatment provider immediately if suicidal ideation or depression develops or if symptoms of acute hepatitis or liver failure emerge (in the case of naltrexone and disulfiram).

Integration of Pharmacotherapy With Nonpharmacological Treatments

Nonpharmacological approaches to treating AUD have long been the standard in the field, whether in a clinical setting or in a self-help group. Essentially all of the clinical trials covered in this chapter either evaluated a medication given in addition to the routine AUD treatment patients would ordinarily receive in that setting or used a manual-guided form of behavioral therapy--for example, AlcoholFree (Mason and Goodman 2005), motivational enhancement therapy (MET; Miller *et al.* 1995), cognitive-behavioral coping skills therapy (Kadden *et al.* 1995), or 12-step facilitation therapy (Nowinsky *et al.* 1992).

The goal of most pharmacotherapy trials was to demonstrate that behavioral therapy combined with medication had a higher rate of treatment response than behavioral therapy combined with placebo. Meta-analyses have shown that on average pharmacotherapies for AUD have a small but significant treatment effect size relative to placebo in patients provided with concomitant behavioral therapy (Jonas *et al.* 2014). Efforts to identify phenotypes, genotypes, and biomarkers predictive of response (described previously) are aimed at guiding the selection of a pharmacotherapy to optimize the likelihood of response for a given patient. However, it is common to associate pill and cure, and medication should be presented as one tool in a toolkit of evidence-based treatments for AUD. Yet some members of self-help groups have criticized members who take AUD medication as not having a true, drug-free recovery. None of the pharmacotherapies for AUD are alcohol-substituting drugs in the way that methadone is for heroin, and this criticism reflects a lack of understanding of drug mechanisms. Physician members of Alcoholics Anonymous (AA) composed a pamphlet that patients can access online advising that AA members "not play doctor" and offering useful guidelines for discriminating appropriate from risky use of medications in patients with AUD and other drug use disorders (Alcoholics Anonymous 2018).

Medications can help restore normal brain functioning, reduce relapse risk, and decrease symptoms of protracted withdrawal (e.g., craving), thereby facilitating the patient's engagement in behavioral treatment. Behavioral therapies in turn enhance the pharmacotherapy response by modifying the patient's attitudes and behaviors related to alcohol, increasing healthy life skills, and helping them stay engaged in treatment.

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcohol Treatment Navigator (https://alcoholtreatment.niaaa.nih.gov) is a website designed to assist in locating clinicians who provide evidence-based behavioral and/or pharmacological treatments for AUD (National Institute on Alcohol Abuse and Alcoholism 2017). Integrating pharmacological and behavioral treatments for AUD increases the likelihood of patients meeting their goals for treatment.

Treatment Response and Recovery

Assessing Treatment Response

A self-report of the number of standard drinks consumed daily combined with a biochemical measure of alcohol intake is used for assessing AUD pharmacotherapy response. Urine dipstick measures of alcohol glucuronide and handheld analyzers of alcohol in expired breath can provide a direct indication of alcohol use near the time the sample is collected. However, given the fast metabolism of alcohol, its use cannot be detected in breath, urine, or plasma over an extended time interval between clinic visits. Indirect biomarkers of alcohol use between clinic visits (e.g., GGT, mean corpuscular volume, and carbohydrate-deficient transferrin) have limitations with regard to sensitivity and/or specificity that can contribute to over-or underestimation of alcohol use. Direct and indirect biomarkers of alcohol use are often used in combination to support the validity of self-reported data.

The gold standard for self-reporting of alcohol use is a standardized interview in a calendar format, typically a variation of the Timeline Followback Interview (Sobell and Sobell 1992), which uses prompts such as weekend versus weekdays, paydays, or holidays to assess the quantity and frequency of alcohol consumption between clinic visits using a *standard* drink metric (see Figure 55-2). One standard drink is defined as containing about 14 g (0.6 fluid ounces) of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, and 1.5 ounces of distilled spirits. Computerized administration is also available to encourage accurate reporting by patients. As an alternative, patients may record their alcohol use on a smartphone app (e.g., AlcooQuizz [Bertholet *et al.* 2019[]) or keep a daily diary of dose(s) taken, abstinence or drinking, and the circumstances associated with a drinking episode. Reviewing these data with the patient at clinic visits may facilitate treatment outcomes by monitoring their progress and identifying high-risk occasions for relapse and strategies for coping. With the patient's permission, periodic interviews with their significant other may be used to validate their self-report of alcohol use, medication adherence, adverse drug effects, and general functioning.

Remission and Recovery

DSM-5 includes specifiers of remission for individuals whose symptoms previously met criteria for AUD but who have experienced none of the symptoms (except craving) for at least 3 and less than 12 months (for early remission) or for 12 months or longer (for sustained remission). NIAAA has recently proposed a new definition of recovery that expands on DSM-5 remission criteria to also include cessation of heavy drinking as a non-abstinence recovery outcome (National Institute on Alcohol Abuse and Alcoholism 2022b). Cessation of heavy drinking is associated with improved social functioning and quality of life, which in turn enhances and sustains remission (Hagman *et al.* 2022). Thus, recovery is conceptualized clinically both as an outcome and as an ongoing process.

Medication Management Issues

Medication Adherence

Medication nonadherence is a common factor influencing pharmacotherapy outcomes across many conditions, including AUD. When it occurs, factors such as adverse drug events or problems managing the dosing schedule should be assessed. Standard measures to ensure adherence may include instructing patients to set reminders on their smartphones and to package their medication in OTC weekly pill trays with the day and time of day indicated for each dose. Identify frequently missed doses by asking patients to bring their pill tray and unused medication at every visit, and link commonly missed doses with an activity of daily living such as eating meals or brushing teeth as a reminder to then take their medication. As an alternative, a Bluetooth-enabled medication management system can alert patients to take scheduled doses and automatically record when doses were taken or missed; this information can be shared electronically with their treatment provider. Patients can reaffirm a commitment to their recovery with every dose taken.

Treatment Duration

There is little scientific evidence to guide the optimal duration of pharmacological treatment of AUD. A patient's history of relapses and the potential consequences of a relapse, the severity of AUD at baseline, and the patient's clinical response and side effects may be determining factors. These factors should be probed if a patient indicates a wish to discontinue treatment before remission and a stable recovery has been established.

Nonresponse or Partial Response to Treatment

An option for nonresponse to treatment may be to switch to an alternative AUD medication, barring any medical contraindications. Partial response to an adequate trial at the recommended dosage of a medication is a challenge. If a relapse to heavy drinking occurs among patients taking acamprosate or naltrexone, they should be instructed to continue taking the medication as prescribed. Relapses may be briefer in duration and less severe if these medications are continued, and neither medication interacts with alcohol. Alternatively, a patient may have reduced his or her drinking by half from baseline but may continue to have episodes of heavy drinking. One may consider the use of combined treatments on a case-by-case basis. There are data that lend support to the safety of acamprosate combined with naltrexone or disulfiram (Besson *et al.* 1998; Johnson *et al.* 2003; Jonas *et al.* 2014; Mason *et al.* 2002), but efficacy data are insufficient to support a general recommendation for combined use as a first-line approach to treating AUD (American Psychiatric Association 2017). Given a potentially increased risk of hepatotoxicity when naltrexone and disulfiram are used in combination, this combination is rarely considered.

Special Populations

Women

A national 2021 survey (Substance Abuse and Mental Health Services Administration 2021a) found that 13 million American women (9.1%) had symptoms that met criteria for AUD in the past year. A review of survey data showed that alcohol use in women is increasing to the point that male and female drinking patterns are now converging (Substance Abuse and Mental Health Services Administration 2021a; White *et al.* 2015). However, with comparable alcohol intake, women are more likely than men to experience a variety of alcohol-related harms, including liver damage, cardiac disease, cognitive deficits, breast cancer, and other health problems, in part because of gender differences in total body water and alcohol metabolism (Bradley *et al.* 1998; Greenfield 2002). Binge drinking among women (defined as consuming four or more drinks in a row) may confer increased risk of accident, rape, assault, and unprotected sex (Wechsler *et al.* 1995). Among individuals with AUD, depression and anxiety disorders, with the associated risk of suicidality, are also more prevalent among women than among men (Conway *et al.* 2006). Alcohol use by pregnant women can have profound effects on the developing fetus. These effects can lead to a range of impairments, including fetal alcohol spectrum disorders, which are characterized by intellectual disability, speech and language delays, social skills deficits, and sometimes facial deformities. Despite the broader range of increased harms of alcohol misuse in women relative to men, women are less likely than men to receive AUD treatment (Gilbert *et al.* 2019). Given the significant disease burden of AUD in women, early intervention and effective treatment options are clearly needed.

A sex-specific meta-analysis of individual records obtained from 1,317 women and 4,794 men who participated in 22 acamprosate clinical trials found a significantly greater effect of acamprosate relative to placebo on rates of abstinence and no heavy drinking, and effect sizes did not differ between men and women (Mason and Lehert 2012). Despite a history of significantly more anxiety, depression, suicide attempts, drug abuse, interpersonal loss, and greater liver impairment at baseline than men, women responded comparably well to AUD treatment. The side-effect and tolerability profile of acamprosate was comparable to that of placebo in terms of number, type, and severity of adverse events and did not differ between women and men. Acamprosate was also associated with significantly higher rates of treatment completion and medication compliance than placebo among both women and men. Potential differences in drug metabolism due to sex hormones or race (e.g., the flushing response to alcohol), and consequent effects on drug efficacy or safety, point to the need for adequate diversity, equity, and inclusion in AUD clinical trials.

Pregnant Women

Disulfiram, naltrexone, acamprosate, and gabapentin are Pregnancy Category C; topiramate is Pregnancy Category D. There are no adequate or well-controlled studies of AUD medications in pregnant women. It is generally recommended that AUD medications not be used during pregnancy, unless acute alcohol withdrawal is being treated with benzodiazepines (American Psychiatric Association 2017).

Nursing Mothers

Topiramate and gabapentin are secreted in human milk; it is not known whether acamprosate, disulfiram, and naltrexone are excreted in human milk. Caution should be used when administering topiramate, gabapentin, acamprosate, or naltrexone to a nursing woman, and disulfiram should be avoided (Alkermes 2010; Duramed Pharmaceuticals 2013; Merck Sante 2005; Teva Pharmaceuticals USA 2015).

Children

Drinking is illegal before the age of 21 years in the United States, and alcohol misuse rather than AUD of moderate or greater severity is more characteristic of this age group. Nevertheless, it is never too early (or too late) to treat AUD. Small (N = 26) double-blind, placebo-controlled studies in adolescents have reported good tolerability and higher rates of abstinence with acamprosate and disulfiram relative to placebo (Niederhofer and Staffen 2003a, 2003b).

Adults Ages 65 and Older

Patients older than 65 years have been included in some clinical trials of disulfiram (De Sousa and Jagtap 2009), naltrexone (Garbutt *et al.* 2005), and acamprosate (Mason *et al.* 2006), but not in sufficient numbers to analyze differences in safety and efficacy from younger patients. Older patients may be at increased risk for hepatic, renal, or cardiac problems; other disorders; or use of concomitant medications that may affect the choice of pharmacotherapy for AUD and indicate a need for close monitoring.

Individuals With Co-Occurring Alcohol Use Disorder and Another Psychiatric Disorder

AUD is the second most commonly identified mental disorder among suicide completers worldwide; the most common is mood disorder (Cavanagh *et al.* 2003). When AUD and mental disorders co-occur, suicide risk may increase--for example, depression may promote increased alcohol intake; alcohol may promote dysphoria, hopelessness, impaired problem solving, and aggression. Concurrent treatment of co-occurring disorders associated with suicide risk, such as depression and AUD, is indicated to reduce the risk of suicide. Meta-analyses suggest that women with AUD have about a sixteen-fold increased risk for suicide compared with women in the general population, whereas men with AUD have about a ninefold increased risk of suicide compared with men in the general population (Kaplan *et al.* 2013). Acute alcohol use can be a powerful precipitant for suicidal behavior, and suicide risk increases with the amount of alcohol consumed (Conner and Bagge 2019). For example, 24% of male suicide decedents and 17% of female suicide decedents were found to have postmortem BAC levels exceeding 0.08g/dL (Kaplan *et al.* 2013). The marked association between AUD and suicide risk underscores the necessity of diagnosing and effectively treating AUD.

Assessment and Treatment of Psychiatric Disorders in Patients With Alcohol Use Disorder

An accurate psychiatric diagnosis cannot be made when a patient is drinking or withdrawing from alcohol; alcohol may reduce some psychiatric symptoms, and conversely symptoms of anxiety and depression may be mistaken for withdrawal instead of an underlying disorder that requires independent treatment. Symptoms of psychiatric disorders should lead to further integrated assessment and treatment planning, with both AUD and co-occurring disorders considered primary disorders. Patients with AUD and concurrent disorders may benefit from a chronic care management approach that includes evidence-based behavioral and pharmacological treatments; social support services; and clinical monitoring of adverse events, medication adherence, and symptoms of relapse. It is important to work collaboratively with the patient and involved significant others, communicate the risks and benefits of each treatment option relative to the patient's recovery goals, and ensure that the patient comprehends this information. The selection of psychiatric medications for patients with AUD requires consideration of abuse potential and potential interactions with other medications, tobacco, illicit drugs, and alcohol, which may affect drug metabolism and safety and warrant enhanced monitoring.

Effects of Acamprosate or Gabapentin on Other Psychotropic Medications and on Sleep

Acamprosate and gabapentin are not metabolized in the liver, and thus drug-drug interactions via cytochrome P450 inhibition are unlikely. The pharmacokinetics of acamprosate are not altered by coadministration with an anxiolytic, an antidepressant medication, or alcohol (Rosenthal *et al.* 2008), which suggests that acamprosate can be used safely by patients with AUD who are receiving concomitant medications for concurrent psychiatric disorders.

Several studies have suggested that acamprosate and gabapentin may help normalize the underlying neurobiological mechanisms of alcohol-related disturbances in sleep (Bazil *et al.* 2005; Staner *et al.* 2006). Sleep disturbances are a challenge often faced by recently detoxified patients. A polysomnography study showed that acamprosate improved sleep continuity, restored N3 (slow-wave) sleep, and increased rapid eye movement sleep latency, all of which are classically described as important determinants of relapses (Brower *et al.* 2001). Another polysomnography study showed that gabapentin decreased N1 sleep and arousals while increasing N3 sleep and sleep efficiency relative to placebo in subjects pretreated with alcohol (Bazil *et al.* 2005). Subjective sleep data obtained from randomized controlled trials lend clinical support to these polysomnography findings (Mason *et al.* 2018; Perney *et al.* 2012, 2015), and a beneficial effect of acamprosate and gabapentin on sleep may be particularly germane to co-occurring disorders in which sleep disruption is a factor (e.g., depression, anxiety, posttraumatic stress disorder).

Use of Psychotropic Medications in Individuals With Comorbid Alcohol Use Disorder

Practice guidelines recommend that antidepressant medication and benzodiazepines not be used for the treatment of AUD unless there is a concurrent disorder for which these are indicated treatments or unless benzodiazepines are used to treat acute alcohol withdrawal (American Psychiatric Association 2017). Patients with AUD and concurrent major depressive disorder have been found to respond to a range of antidepressant medications (Mason *et al.* 1996; McGrath *et al.* 1996; Pettinati *et al.* 2010; Roy-Byrne *et al.* 2000). Conversely, the use of antidepressant medication to reduce drinking relapse is generally not supported in patients with AUD who are not depressed (Cornelius et al. 2009; de Bejczy and Soderpalm 2015; Friedmann *et al.* 2008; Gorelick and Paredes 1992; Kabel and Petty 1996; Mason *et al.* 1996; Naranjo *et al.* 1990).

Similarly, the use of antipsychotics to reduce the risk of drinking relapse is not supported as a first-line treatment for AUD but may be particularly useful for patients with AUD who have a concurrent disorder for which the drugs are indicated (Anton *et al.* 2008a; Bender *et al.* 2007; Brunette *et al.* 2020; Green *et al.* 2015; Mohamed *et al.* 2015). Bipolar disorder with concurrent AUD can be effectively treated with mood-stabilizing medications (e.g., lithium, quetiapine, valproate), and benefit is also shown for drinking outcomes (Brown *et al.* 2008; Salloum *et al.* 2005). The use of mood-stabilizing medications to reduce the risk of drinking relapse is not effective in patients with AUD who do not have concurrent bipolar disorder (Brown *et al.* 2008, 2014; Fawcett *et al.* 2000; Litten *et al.* 2012).

Anxiety disorders with concurrent AUD respond to some antianxiety medications, such as sertraline (Brady *et al.* 1995) and paroxetine (Book *et al.* 2008; Thomas *et al.* 2008), but not to others, such as venlafaxine (Ciraulo *et al.* 2013). The use of an antianxiety medication to reduce the risk of drinking relapse in patients with AUD who do not have anxiety disorders was not found to be effective in a double-blind, placebo-controlled trial of buspirone (Fawcett *et al.* 2000).

Individuals With Co-Occurring Alcohol Use Disorder and Another Substance Use Disorder

Concurrent Alcohol Use Disorder and Opioid Use Disorder

Naltrexone (oral and injectable) is FDA approved both for the treatment of AUD and for the prevention of relapse in patients with opioid use disorder (OUD) following opioid detoxification. Patients with AUD and concurrent OUD who wish to remain opioid free and to cut down on or quit drinking can receive this single treatment for both disorders in conjunction with a comprehensive management program that includes psychosocial support. Naltrexone is an opioid antagonist and will induce withdrawal in patients who use opioids; therefore, patients must not be using prescribed or illicit opiates when starting naltrexone treatment. Patients receiving Vivitrol must be opioid free for 7-10 days before treatment. It is vital for patients to comprehend that attempting to overcome the blockade produced by naltrexone by taking opioids is very dangerous and may lead to a fatal overdose. Similarly, the use of lower dosages of opioids after Vivitrol is discontinued, at the end of a Vivitrol dosing interval, or after missing a Vivitrol dose could result in life-threatening opioid intoxication (e.g., respiratory arrest and circulatory collapse). Acamprosate is not a treatment for OUD but, unlike naltrexone, may be used safely by patients with concurrent AUD and OUD who choose opioid substitution therapy with methadone or buprenorphine.

Concurrent Alcohol Use Disorder and Nicotine Use Disorder

Varenicline (Chantix) is a partial a4b2 nicotinic acetylcholine receptor agonist that was approved by the FDA as a treatment for smoking cessation in 2006. A number of double-blind, placebo-controlled clinical trials have reported a reduction in alcohol consumption in heavy-drinking smokers treated with varenicline 2 mg/day (Bold *et al.* 2019; Hurt *et al.* 2018; Mitchell *et al.* 2012; O'Malley *et al.* 2018). Importantly, varenicline showed positive effects for the treatment of AUD in a multicenter double-blind,

placebo-controlled clinical trial, in which it lowered the weekly percentage of heavy-drinking days, drinks per drinking day, and alcohol craving compared with placebo (Litten *et al.* 2013). Effects on drinking occurred in both nonsmokers and smokers, which suggests a direct effect on AUD; thus, varenicline is an appealing potential choice for patients seeking treatment for concurrent AUD and smoking cessation. The finding that varenicline decreases alcohol consumption in AUD was replicated in secondary analyses of a Swedish multicenter clinical trial (de Bejczy *et al.* 2015). Of note, a recent double-blind trial that compared combination treatment with varenicline and naltrexone versus varenicline monotherapy in heavy-drinking smokers found significantly greater smoking abstinence with varenicline monotherapy than with the varenicline-naltrexone combination (Ray *et al.* 2021).

Novel Medications Focused on Negative Emotional States in Alcohol Use Disorder

Much of the previous work on medications for AUD was focused on blocking the rewarding effects of drugs in the binge/intoxication stage of the AUD cycle, but identifying a clear role for the motivational signs of withdrawal, as reflected by negative emotional states in the withdrawal/negative affect stage, represents a compelling rationale for focusing on neurobiological targets in this domain.

Some of these potential neurobiological targets have advanced to clinical testing. For example, mifepristone, which acts as a glucocorticoid receptor antagonist, was found to decrease craving and drinking in recently abstinent participants with AUD in a human laboratory model of protracted withdrawal (Vendruscolo *et al.* 2015) and is now under study in a randomized controlled trial. Glucocorticoid receptor signaling in the hypothalamic-pituitary-adrenal axis and extrahypothalamic system may be a potential target for drug development because of a putative dual role (i.e., to normalize reward function and desensitize stress systems).

Vasopressin is a pro-stress, dysphoria-inducing brain neurotransmitter system that converges on the extended amygdala and contributes to negative emotional states associated with protracted withdrawal (Koob 2008). An investigational vasopressin V_{1b} receptor antagonist, ABT-436, was found to increase the rate of abstinence in a multicenter trial of AUD. Furthermore, participants who reported high levels of stress responded better, as evidenced by decreases in both the frequency of drinking and the number of heavy drinking days (Ryan *et al.* 2017).

These trials, combined with others involving gabapentin, lend support to the hypothesis that desensitization of brain stress systems mediates the negative emotional states in protracted withdrawal and offer a valid pharmacological target for treatment of AUD. A complementary pharmacological approach would be to activate anti-stress buffering systems in the brain as a strategy for restoring homeostasis in protracted withdrawal (Koob 2008).

Oxytocin, a neuropeptide that is emerging as a stress buffer, is currently under clinical investigation for the treatment of AUD and withdrawal. Preliminary work showed that intranasal oxytocin was superior to placebo at reducing symptoms of relatively mild alcohol withdrawal (Pedersen *et al.* 2013) and had a dual effect on alcohol craving in a human lab study; more socially anxious subjects who abused alcohol showed decreased

craving, and less socially anxious subjects showed increased craving, with oxytocin relative to placebo (Mitchell *et al.* 2016).

The recent surge in understanding of the neurocircuitry and neuropharmacological mechanisms involved in withdrawal/negative affect and relapse in AUD has provided abundant targets for the development of future medications for treating AUD, as was shown in Figure 55-3. Both repurposed drugs, such as gabapentin, varenicline, and mifepristone, and new molecular entities, such as the vasopressin V_{1b} receptor antagonist, which are all selective for these targets, are showing promise as emerging new treatments for AUD.

Evolving Treatments for Alcohol Use Disorder

Transcranial Magnetic Stimulation

Background and History

Transcranial magnetic stimulation (TMS) is based on the principle of electromagnetic induction developed by the renowned English scientist Michael Faraday during the first half of the nineteenth century (Maxwell 1881). The principle of TMS is rooted in the observation that a brief increase in the flow of an electric current through a coil (a wire in the shape of a spiral that conducts electricity) produces a transient magnetic field. The magnetic stimulators used in TMS work by inducing short electric currents that produce such magnetic fields. In TMS therapy, these magnetic fields are allowed to pass freely into the skull. Because the neurons underneath function like electrical conductors, the propagation of magnetic fields in neurons causes the electric current to flow, exciting or inhibiting neural activity.

Electricity and magnetism are two intertwined and very powerful forces in the universe. There is no magnetism without electricity, and there is no electricity without magnetism. Magnetism is one of the four fundamental forces in nature. Our planet's magnetic field protects the earth by deflecting solar winds. In medicine, the healing properties of magnets were recognized in Ancient Egypt as early as 3200 b.c. Much later, in the 17th century, the English physician William Gilbert allegedly used magnets to relieve the arthritis of Queen Elizabeth I. Today powerful magnets are harnessed to acquire very detailed images of our bodies and our brains with a technology called MRI.

Over the past few centuries, numerous scientists from all over the world have contributed to the development of the science behind the current applications of TMS, from Luigi Galvani (1737-1798), one of the founders of modern electrophysiology, in the eighteenth century to Anthony Barker, who in 1985 developed the prototypes of the so-called Sheffield magnet, which is considered the first TMS device, in the twentieth century (Horvath *et al.* 2011). TMS uses pulsed magnetic fields that are concentrated in an area the size of a small coin. These pulses are generated by a magnetic coil placed on the scalp, allowing precise, noninvasive application over the head. By applying repeated stimulation pulses, repetitive TMS can gradually increase or decrease the activity of specific regions of the brain, such as the dorsolateral prefrontal cortex (dlPFC). The dlPFC plays an important role in AUD and other addictions because this region functions as a neural hub, connecting key brain areas involved in motivation, decision-making, and the ventral tegmental area/dopamine reward system. When the magnetic field delivered by a medical TMS device reaches the cortex, neurons react by generating action potentials, thereby modulating neuronal activity not only within the target region (e.g., the dlPFC) but also in downstream regions to which the target area is connected.

Transcranial Magnetic Stimulation as a Novel Therapy for Alcohol Use Disorder

AUD is a major public health problem around the world. Although effective medications and psychological interventions exist for the treatment of AUD and can reduce harmful alcohol consumption, even with treatment many people with AUD continue to experience challenges with controlling alcohol craving and remain vulnerable to relapse.

As in other addictions and SUDs, many areas of the limbic system, and specifically the frontal cortical regions, are involved in the expression of pathological behaviors associated with AUD, both in animal models and in humans (Rudebeck and Izquierdo 2022). Meta-analyses have revealed significant bilateral gray matter reductions in medial cortical regions across the cingulate and superior frontal gyri, the precuneus, and insular cortices as well as the thalamus, amygdala, and cerebellum in patients with AUD (Spindler *et al.* 2021). These gray matter reductions correspond to behavioral changes, including compromised cognition, emotion processing, and somatosensory and motor functioning, following long-term alcohol misuse (Spindler *et al.* 2021).

Evidence of the ability of TMS to significantly reduce craving and relapse to AUD and other SUDs, in particular cocaine use disorder, has been accumulating for several years (Lolli *et al.* 2021; Madeo *et al.* 2020; Terraneo *et al.* 2016). With respect to AUD, repetitive TMS applied to the right dlPFC suppressed alcohol craving following recent detox (Belgers *et al.* 2022). Similarly, deep TMS reduced craving and the proportion of heavy drinking days compared with sham TMS in people with AUD (Harel *et al.* 2021). Active deep TMS was also linked to decreased functional connectivity among the anterior cingulate cortex, caudate nucleus, and medial prefrontal cortex in people with AUD (Harel *et al.* 2021). On the basis of these and other studies, in 2021 a TMS device received *conformite europeenne* approval in the European Union for the treatment of addiction (Cision PR Newswire 2021).

Interestingly, a significant percentage of patients treated for cocaine use disorder also experience co-occurring AUD. In some reports, up to 85% of people with cocaine use disorder also have symptoms that meet criteria for lifetime AUD (Regier *et al.* 1990). In our experience, the majority of patients initially receiving TMS therapy for cocaine use also report a reduction in alcohol craving and relapse. Going forward, applications of TMS therapy for polysubstance use must be explored.

Taken together, these data suggest that TMS may be a new approach to helping patients with AUD by reducing craving and heavy drinking and mitigating relapse. Given the need for additional effective therapies for AUD and the precedent set in Europe, TMS may move forward for approval for this indication in the United States, as it has for treatment-resistant depression. In addition, with its mild side-effect profile, TMS may be a promising treatment for pregnant women with AUD (Martinez-Gras *et al.* 2021; Pridmore *et al.* 2021).

Ketamine

The history of ketamine begins in the 1950s in the United States. Today this very interesting molecule is gaining increasing attention thanks to its varied potential therapeutic applications. Ketamine was originally discovered in Detroit, Michigan, where scientists at Parke-Davis were focusing their efforts on a quest for the ideal anesthetic agent, which, aside from being a safe anesthetic, would also have the ability to produce analgesia. The discovery of ketamine dates to 1962, when it was originally called CI-581 (2-[O-chloro-phenyl]-2-methyl-amino cyclohexanone). The name *ketamine* derives from the words *ketone* and *amine*, based on its molecular structure. The first human administration of ketamine was in 1964, only 2 years after its discovery, to volunteer subjects in prisons (reviewed in Mion 2017). In the 1970s, low doses of ketamine were found to exert analgesic properties (Sadove *et al.* 1971). The anesthetic and analgesic properties of ketamine, together with its anti-inflammatory effects, led to its use on patients in burn centers. However, when ketamine was used as an anesthetic during the Vietnam War, its psychedelic effects began to raise concerns. Ketamine misuse became prevalent during the Vietnam War and began to occur in the United States (Jansen 2000).

Much later, ketamine was found to have unexpected psychiatric applications. In 2000, Berman and colleagues produced the first study highlighting rapid antidepressant effects of ketamine among patients with major depressive disorder (Berman *et al.* 2000). This report went largely unnoticed until the antidepressant effects of ketamine were replicated a few years later (Zarate *et al.* 2006). Since then, ketamine has received increasing attention in the scientific and medical fields (Souza-Marques *et al.* 2021). Today a PubMed search for ketamine reveals more than 22,000 publications, and a search for ketamine + depression reveals more than 3,700.

From a mechanistic perspective, ketamine has been shown to have a variety of effects on glutamatergic receptors, in particular *N*-methyl-D-aspartate (NMDA) and a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, as well as on glutamate release (Aleksandrova *et al.* 2017). These mechanisms of action are among the major reasons why ketamine has received so much attention from the scientific and clinical communities as a potential therapy for AUD. In support of ketamine's utility as a novel treatment for AUD, a study by Dakwar *et al.* (2020) indicated that a single infusion of ketamine significantly reduced the likelihood of heavy drinking, enhanced the likelihood of abstinence, and delayed the time to relapse, particularly when patients also underwent MET. Similarly, a recent study showed that three weekly infusions of ketamine combined with psychological therapy increased the number of days of abstinence from alcohol consumption (although relapse rates were similar between placebo and ketamine groups [Grabski *et al.* 2022]). These studies highlight the potential of ketamine for reducing alcohol drinking and increasing abstinence among people with AUD who receive concomitant personalized behavioral therapy (e.g., MET). Although future studies are indicated to identify optimal ketamine and psychological therapy regimens for AUD, it is plausible that a wide variety of infusion frequencies and dosages adapted to the medical and personal histories of each patient will be necessary to maximize ketamine's therapeutic utility.

Psilocybin

In addition to ketamine, a chemical compound found in mushrooms of the genus *Psilocybe*, psilocybin (which has psychedelic properties), is gaining increasing attention as a potential aid for a variety of psychiatric conditions ranging from depression to AUD and other addictions (Davis *et al.* 2021; Gukasyan *et al.* 2022; Nutt and Carhart-Harris 2021). Fungi like *psilocybin* mushrooms have been on earth for millions of years. One of the most intriguing theories surrounding the origins of psilocybin use postulates that almost 2 million years ago, *Homo erectus* achieved altered states of consciousness from eating mushrooms containing psychedelic compounds (McKenna 1992). Independent of this theory, populations spanning from Siberia to Greece to Central America are known to have used psychedelic mushrooms in rituals to foster unity and emotional and spiritual closeness between community members as well as with higher powers of the universe.

From a mechanistic perspective, two of the primary sites of psilocybin's actions are the serotonin and glutamate systems (Martin-Ruiz *et al.* 2001;

Nichols 2016). The neurobiological effects of psilocybin may in part explain the growing evidence that psilocybin-assisted therapy has important antidepressant and antianxiety effects on individuals with life-threatening cancer, treatment-resistant depression, and/or anxiety. In contrast to ketamine, which has high abuse liability and requires rigorous medical monitoring, psilocybin is relatively easier to manage, monitor, and administer to patients. Thus, psilocybin-assisted therapy has recently been explored as a novel antidepressant treatment (Carhart-Harris *et al.* 2016; Goldberg *et al.* 2020; Griffiths *et al.* 2016; Ross *et al.* 2016). However, clinical trials have emphasized the need for psychological therapy and a controlled setting with health care professionals when using psilocybin as a putative treatment (Davis *et al.* 2021; Gukasyan *et al.* 2022).

With respect to AUD, a 2015 study suggested that psilocybin has therapeutic potential in mitigating alcohol use (Bogenschutz *et al.* 2015). In this pilot study, 10 volunteers with DSM-IV alcohol dependence received orally administered psilocybin in one or two supervised sessions in combination with MET, as well as additional therapy sessions focused on explaining the psilocybin sessions. Although abstinence from alcohol use did not change significantly in the first 4 weeks of observation (before the subjects received psilocybin), abstinence increased significantly following psilocybin administration. Furthermore, the apparent effects of psilocybin on suppressing alcohol use were maintained for up to 36 weeks at follow-up. These observations, albeit preliminary, warrant further study aimed at understanding the potential therapeutic use and risks of psilocybin as an additional therapy to help initiate and maintain alcohol abstinence.

In conclusion, psychedelic compounds like ketamine and psilocybin may offer therapeutic options for patients with a variety of treatment-resistant psychiatric conditions from depression to AUD and other addictions (Nielson *et al.* 2018). Future studies are needed to delineate patient selection criteria and treatment regimens, indications, contraindications, risks, and overall treatment costs for patients with these devastating conditions.

Effects of the Pandemic on Alcohol Use and Treatment for Alcohol Use Disorder

The United States declared the SARS-CoV-2 virus a public health emergency on January 31, 2020. This pandemic changed the relationship many individuals had with alcohol. The protracted stress of the pandemic, and pandemic-related constraints on healthy coping mechanisms such as social gatherings or gym workouts, led many to increase their alcohol use as a coping strategy or as self-medication for pandemic-related increases in depression and anxiety (Capasso *et al.* 2021). Stress is likely to increase alcohol use, whether it derives from social isolation, personal and financial losses, or a large-scale disaster (Grossman *et al.* 2020; Koob *et al.* 2020). Alcohol may provide short-term relief from negative emotional states and thereby reinforce its continued use. However, neuroadaptations occur over time that reduce the relief provided by alcohol and increase the experience of negative affective states when not drinking, thereby creating a heightened vulnerability to further increases in alcohol use (Koob *et al.* 2020). COVID-19-related increases in alcohol consumption that are sustained for more than a year are projected to cause marked increases in liver disease and deaths (Julien *et al.* 2022). Similarly, a Rand Corporation study projected that high levels of stress related to the COVID-19 pandemic, isolation, and unemployment could account for an unprecedented surge in "deaths of despair" caused by alcohol, drugs, and suicide (Petterson *et al.* 2020).

One stark example of the association between the pandemic and alcohol misuse can be found in an analysis of U.S. mortality data from the National Center for Health Statistics. These data showed an average of 8,251 alcohol-related deaths per month in 2020 compared with 6,256 in 2018 and 6,577 in 2019 (White *et al.* 2022). The primary causal factors for 2020 alcohol-related deaths included alcohol-associated liver disease (29.8%), overdose (18.1%), and AUD and withdrawal (15.4%). Whether the increase in pathological alcohol use observed during the pandemic will persist after the pandemic is not yet known. However, studies following people in the 9/11 World Trade Center Health Registry found increased risk of pathological drinking lasting more than a decade after exposure to the 9/11 attacks (Welch *et al.* 2017). These findings suggest that treatment providers may see an unprecedented number of individuals presenting for treatment for AUD and alcohol-related problems.

A unique sequela of the COVID-19 pandemic involved constraints on in-person clinical assessment and treatment to mitigate the spread of COVID-19 infection among patients and practitioners. Interventions to help people cope with an unhealthy relationship with alcohol could not be deferred until the pandemic subsided, in particular given the increased risk of suicide when AUD co-occurs with depression and other serious mental disorders (Chiappini *et al.* 2020). Delivering AUD treatments safely and effectively during the pandemic involved the rapid adoption of telehealth modalities for individuals experiencing ongoing obstacles to in-person treatment, and these strategies have increasingly been incorporated into routine care as pandemic constraints have relaxed.

Telehealth Strategies to Facilitate Pharmacological Treatment of Alcohol Use Disorder

Overview

The use of telehealth strategies to facilitate the identification of and intervention for alcohol misuse was increasing prior to the pandemic and expanded rapidly during the pandemic. Notably, the CDC issued a call in March 2020 for nonemergent medical care to prioritize telehealth consultations. Thus, telehealth modalities proved essential in meeting an increased need for diagnosis and treatment of AUD during the pandemic and is now part of routine postpandemic AUD treatment options. A defining feature of telehealth is that assessments and interventions are conducted remotely. Technologies currently available to facilitate evidence-based treatments of AUD include

telephone and videoconferencing calls, internet-based self-guided programs, smartphone apps, and biosensor monitoring devices (Table 55-3). AA provides a free AA Meeting Guide smartphone app with information on the day, time, and location of in-person and Zoom meetings near the current location of the app user as well as a link to access a selected Zoom meeting. Similarly, the websites of secular mutual support groups (e.g., SMART Recovery, LifeRing Secular Recovery, and Women for Sobriety) currently provide calendars of in-person and virtual Zoom meetings (Bergman *et al.* 2021).

TABLE 55-3. Examples of evidence-based telehealth options that may be used in conjunction with pharmacological treatment of alcohol use disorder

Websites
Rethinking Drinking: www.rethinkingdrinking.niaaa.nih.gov
NIAAA Alcohol Treatment Navigator: https://alcoholtreatment.niaaa.nih.gov
NIAAA Healthcare Professional's Core Resource on Alcohol: https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol
Video conferencing or telephone
Screening, Brief Intervention, and Referral to Treatment
Virtual and in-person mutual support meetings
* Alcoholics Anonymous
* SMART Recovery
* LifeRing Secular Recovery
* Women for Sobriety
Smartphone apps
AlcooQuizz

Note. NIAAA = National Institute on Alcohol Abuse and Alcoholism; SCRAM = Secure Continuous Remote Alcohol Monitor.

[a] Fee-based self-administered programs. CBT4CBT and CheckUp & Choices must be prescribed as components of a treatment plan led by a health professional.

Alcoholics Anonymous Meeting Guide
Apple Health app
BACtrack app
Devices
Bluetooth-enabled BACtrack Mobile Breathalyzer with smartphone app
SCRAM Continuous Alcohol Monitoring ankle bracelet
LiveFine Smart WiFi Automatic Pill Dispenser
Proprietary online interactive programs[a]
CBT4CBT
CheckUp & Choices
Tempest Alcohol Recovery and Support to Quit Drinking Program

Note. NIAAA = National Institute on Alcohol Abuse and Alcoholism; SCRAM = Secure Continuous Remote Alcohol Monitor.

[a] Fee-based self-administered programs. CBT4CBT and CheckUp & Choices must be prescribed as components of a treatment plan led by a health professional.

Prior to the pandemic, early studies found support for the efficacy of AUD interventions delivered via teleconferencing as well as a high degree of patient satisfaction with this telehealth modality, especially when transportation and access to treatment are limited (e.g., in rural areas [Campbell *et al.* 2016; Lin *et al.* 2019; Staton-Tindall *et al.* 2014]). Similarly, a pilot study found equivalent efficacy for a self-administered web-based program based on SMART Recovery principles and in-person SMART Recovery participation (Campbell *et al.* 2016). The Hazelden Betty Ford Foundation implemented a pilot virtual intensive outpatient program for 1,446 patients prior to the onset of the pandemic and found treatment outcomes comparable to those of 1,009 outpatients who had received in-person intensive outpatient treatment; results showed increased rates of abstinence, AA attendance, and quality of life (mental and physical) 3 months after discharge (Gliske and Ngo 2020). Of note, patients in the virtual group attended more sessions and had a lower rate of discharge against medical advice than those in the in-person group.

These findings lend support to the acceptability and efficacy of virtual treatment of AUD. In general, fidelity to evidence-based AUD treatments (e.g., MET, CBT, 12-step facilitation therapy, and dialectical behavior therapy) as opposed to general supportive psychotherapy optimizes AUD treatment outcomes, whether treatment is given in person or remotely via telehealth (Kadden *et al.* 1995; Miller and Rollnick 2014; Miller *et al.* 1995; Nowinsky *et al.* 1992). Examples of currently available AUD telehealth tools are provided in the following sections and in Table 55-3.

Websites

The NIAAA Healthcare Professional's Core Resource, launched in Fall 2022, is an online tool that aims to cover the basics of what every healthcare professional needs to know about alcohol (National Institute on Alcohol Abuse and Alcoholism 2022c). It offers free continuing medical education/continuing education credit for 14 educational modules that include a guide to SBIRT, brief interventions, and evidence-based treatments for AUD.

NIAAA has also developed an easy-to-navigate evidence-based online resource for clinicians, patients, and their families called Rethinking Drinking (National Institute on Alcohol Abuse and Alcoholism 2022b). Topics covered include "How much is too much?" and "Thinking about a change?" and are accompanied by probes to help individuals assess their own readiness for change in their alcohol use. The SBIRT model has been adapted for virtual use by clinicians using phone or video conferencing (National Institute on Alcohol Abuse and Alcoholism 2022a). When in an online meeting, the clinician may screen-share modules of the NIAAA Rethinking Drinking website to guide a brief invention using motivational interviewing. Tools for self-monitoring alcohol use are provided on the Rethinking Drinking website, as are strategies for cutting down or quitting. Links are provided to professional associations of AUD treatment specialists, mutual support groups, and the NIAAA Alcohol Treatment Navigator (https://alcoholtreatment.niaaa.nih.gov).

The Treatment Navigator website provides information on AUD and types of evidence-based AUD treatments and on how to find qualified clinicians who provide evidence-based AUD pharmacotherapy and behavioral treatments (National Institute on Alcohol Abuse and Alcoholism 2017). Links are also provided to CBT4CBT (Carroll *et al.* 2008), a proprietary computer-based CBT program to help people stop or reduce alcohol use that can be prescribed by a health care professional in conjunction with pharmacological treatment as part of a comprehensive AUD treatment plan.

The Tempest Online Alcohol Recovery and Support to Quit Drinking program is an 8-week fee-based, feminine-centric approach to recovery that includes elements of evidence-based treatments for AUD (i.e., CBT, dialectical behavior therapy, mindfulness, and peer coaching). A naturalistic outcome study assessed alcohol use and related outcomes among 541 Tempest participants (Moskal *et al.* 2021). Participants were 94.8% female and 94.3% white; 81% had a college degree or higher, and 96.9% had symptoms that met criteria for AUD. Among those participating in 2-month (58.7%), 6-month (47.9%), and 12-month (24.6%) follow-up assessments, a significant reduction from baseline was found in the number of DSM-5 AUD symptoms, alcohol use, and craving, with general improvement in mental and physical health and quality of life. The highly specific demographics of the participants in the Tempest study (i.e., white, educated females) are a reminder that such factors may influence an individual's attitude toward alcohol use and treatment. Cultural competence in understanding the influence of such factors may facilitate building a therapeutic alliance and providing optimal telehealth referrals.

Smartphones

It is estimated that 97% of U.S. adults own a cell phone (Pew Research Center 2021). Text messaging of appointment reminders is widely used in medicine to decrease the frequency of missed appointments. Text messaging can support recovery by transmitting motivational affirmations and relapse prevention support. Smartphones may also be used to set medication reminders, find mutual support meetings, and track alcohol use. Systematic reviews of smartphone apps targeting alcohol use have found few commercially available options that have been scientifically evaluated for efficacy (Colbert *et al.* 2020) or that integrate evidence-based interventions for AUD (Tofighi *et al.* 2019). App features that have face validity include a baseline assessment of alcohol use and subsequent tracking of drinking, geospatial positioning locators of 12-step meetings and AUD treatment programs, and warnings about proximity to locations with increased risk of drinking. Evidence of efficacy was provided for AlcooQuizz, a free-to-download app that provides individuals with a self-assessment of their drinking relative to age-and sex-adjusted norms, current BAC estimate, and drinking limit challenges; data collected may be shared remotely through the app with a treatment provider. A controlled trial involving 977 participants found that those who downloaded the AlcooQuizz app showed a significant reduction in the number of drinks per week at 6-month follow-up relative to a control group not offered any intervention (Bertholet *et al.* 2019).

Apps for self-monitoring alcohol use can help keep people engaged and mindful of alcohol use goals, in particular those with less severe alcohol problems. However, there is little evidence of efficacy for AUD of greater severity when such apps are used without the supervision and personalized care of treatment professionals (Kaner *et al.* 2017). Clinicians who become familiar with the apps their patients are using will be better able to use app data to discuss patients' progress and relapse risk. Standards for medical devices and cybersecurity also apply to app data shared with clinicians to ensure data security and patient privacy.

Biosensor Devices

Biosensor devices can be used to monitor physiological parameters such as heart rate and to measure chemical levels in the body, such as BAC. BACtrack (KHN Solutions, Inc.; San Francisco, California) is an app that pairs with an OTC Bluetooth-enabled smartphone keychain breathalyzer that can generate detailed drinking data and BAC readings. It can be used by individuals to estimate their BAC, what it means for their level of intoxication and motor skills, and how long it will take to achieve a zero BAC. Data from random or scheduled BAC determinations (e.g., daily at

8:00 p.m.) can be shared remotely via the BACtrack smartphone app with treatment providers to monitor recovery and optimize treatment response (e.g., by identifying risky times for drinking and implementing proactive coping strategies).

The Secure Continuous Remote Alcohol Monitor (SCRAM) is an ankle bracelet that can be worn continuously to monitor transdermal alcohol content every half hour and more frequently when a heavy drinking episode or tampering with the device is detected. Alcohol-related data are uploaded to a secure web-based server. The SCRAM is the only device to measure transdermal alcohol content that is currently commercially available, although flexible wristwatch-like models (e.g., the BACtrack Skyn) are in various stages of development.

Smartphones may be paired with a smartwatch to electronically monitor pulse rate data and share them with a treatment provider (e.g., by using the sharing function on the Apple Health app). These heart rate data can be valuable in remotely assessing risk of clinically significant alcohol withdrawal. Such devices can also collect sleep and activity data that may be electronically shared with a treatment provider to assess behavioral changes that may signal an increased risk of drinking relapse. As an alternative, patients can obtain an OTC digital pulse and blood pressure monitor at a pharmacy or online and show the current reading to their clinician during video appointments.

Bluetooth-enabled medication management systems and apps (e.g., the LiveFine Smart WiFi Automatic Pill Dispenser) can alert patients and/or clinicians to missed doses of AUD medications and deliver systematic reminders to ensure adherence to pharmacological treatment.

Telehealth as a Mainstream Treatment Modality for Alcohol Use Disorder

Surveys of more than 6 million employee health plan beneficiaries conducted in 2019 and 2020 found a 20-fold increase in the utilization of telemedicine after the onset of the pandemic (Cantor *et al.* 2021). Telehealth now offers critical access to AUD screening and intervention for groups that have seen pandemic-related increases in AUD, such as women caring for young children in the home for whom in-person treatment is prohibitive because of child care and transportation constraints (Busch *et al.* 2021).

Telehealth applications for treating AUD are evolving rapidly. Many providers were not prepared to quickly launch a telehealth practice and had to learn--and teach their patients--how to establish a quiet, well-lit, private space and ensure adequate bandwidth and transmission speed for Zoom calls. A backup plan in case of technology failure had to be established, as did strategies to address privacy issues. APA and the American Telemedicine Association provided general guidelines in "Best Practices in Videoconferencing-Based Telemental Health April 2018" (Shore *et al.* 2018). Telehealth for AUD also raised concerns among practitioners about liability, reimbursement, and regulatory issues at the state and federal levels. SAMHSA provided information to address these issues in its evidence-based resource guide *Telehealth for the Treatment of Serious Mental Illness and Substance Use Disorder* (Substance Abuse and Mental Health Services Administration 2021b). This guide also reviews the extant literature and research findings related to telehealth treatment of AUD and related disorders and concludes that telehealth is effective across the continuum of care for AUD, including screening, pharmacotherapy, behavioral treatments, recovery support, and crisis management. No differences in treatment efficacy, retention, or attendance rates, or in patients' level of satisfaction, were found between in-person and telehealth treatments.

Some patients with AUD may prefer to have face-to-face meetings with counselors and mutual support groups and to receive their medication, give urine and breath samples, and get feedback and encouragement in person. But many patients prefer the convenience, reduced stigma, and expanded access to care that telehealth provides while reducing the burden of travel and associated time off from work and need for child care. Telehealth reduces geographic barriers to care as well as barriers imposed by psychological and physical disabilities.

Combining pharmacological treatment of AUD with evidence-based telehealth interventions (see Table 55-3) may optimize AUD treatment outcomes by allowing clinicians to work smarter with continuously updated information from biosensor devices, smartphone apps, and online medication monitoring systems. Incorporating technology into an AUD treatment plan could expand practitioners' caseload capacity by decreasing their travel time to treatment settings, increasing their flexibility in scheduling, and expanding AUD specialty services to general practice settings. Telehealth AUD treatment teams could facilitate more strategic utilization of AUD specialty care services in a hub-and-spoke model that coordinates services and provides for continuity of care.

Research is needed to determine the adequate duration of telehealth treatments, any optimal degree of integration with traditional in-person treatments, and the sustainability of effects. Of note, an analysis of smartphone app data from a cohort of 152 patients who completed AUD residential treatment generated a model with good predictability of relapse risk within the coming week (Chih *et al.* 2014). Future analyses of large app data sets may further identify factors signaling increased risk of drinking relapse and patients who may benefit from immediate personalized support to mitigate their risk. Now that safe and effective telehealth modalities have been widely implemented for the treatment of AUD during the pandemic, consensus best practice recommendations should be developed and systematically implemented in training programs to ensure AUD telehealth continues to be available and is delivered in a safe and effective manner. Future work is

needed to understand the extent to which COVID-19-related changes in telehealth utilization may permanently impact AUD treatment, including identifying barriers and facilitators at the patient, provider, health care system, insurer, and legislative levels (Cantor *et al.* 2021). Pharmacological and behavioral telehealth interventions could potentially reach millions with AUD who currently go untreated as well as offer monitoring and support for those in recovery (e.g., with just-in-time interventions).

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CHAPTER 56

Treatment of Personality Disorders

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Personality disorders are among the most challenging conditions faced by clinicians. The two main approaches to treating personality disorders are psychosocial treatment and medication. Psychotherapy continues to be the treatment foundation for all personality disorders, and psychotherapy studies on the whole have shown improvement with treatment two to four times greater than the improvement seen in control conditions (Perry and Bond 2000). The main indications for using medications in treating personality disorders are periods of decompensation, crises, and hospitalizations; the need for longer-term management of symptom clusters that are maladaptive and may be responsive to medication; and the reappearance or worsening of comorbid conditions. The underlying rationale for medication use in personality disorders is that associated behavioral traits might have neurobiological and psychological correlates (Oquendo *et al.* 2005; Simeon *et al.* 1992).

In this chapter we summarize the literature to date on the pharmacological treatment of personality disorders. We begin with a brief overview of current conceptualizations of personality and what constitutes a personality disorder, followed by a discussion of the treatment of Cluster B disorders (which have the largest evidence base), Cluster A disorders, and Cluster C disorders. Findings from neuroimaging, neuroendocrine, and cognitive-behavioral studies pertinent to the understanding of personality disorders are summarized. The chapter concludes with a brief overview of emerging areas of research and their implications for our understanding of the pathophysiology and treatment of personality disorders.

Models of Personality

Although nobody doubts the existence of personality, what constitutes its disordered form has been controversial. There is little disagreement on the limitations of the current categorical classification of personality disorders, but consensus on a unified model has been lacking. Much of the debate has centered on dimensional versus categorical models of personality disorders. The alternative dimensional model for personality disorders in Section III of DSM-5 (American Psychiatric Association 2013) has two main criteria: impairment in personality functioning and one or more pathological personality traits.

The founder of personality psychology, Gordon Allport (1937), in one of the earliest conceptualizations of personality disorders, theorized that "personality 'is' something and personality 'does' something" (p. 48). In the more than 80 years since then, research into what personality "is" (i.e., trait structural models) has dominated the field (Ro *et al.* 2013). Recently there has been increased attention to what personality "does"--that is, the functional aspects of personality and how it serves to adapt individuals' behaviors to their situations (Ro and Clark 2009). Distinguishing personality functioning from traits is important conceptually, because simply having extreme traits is not necessarily pathological. From an evolutionary perspective, Livesley and Jang (2000) theorized that severe personality pathology reflects a failure of three adaptive systems: a self-system (i.e., the development of a stable concept of self and, correspondingly, of others) and two other-systems (i.e., the capacity for close personal relations and intimacy, and the ability to function effectively at a societal level). The consequence of this system failure is an inability to handle major life tasks, in effect Sigmund Freud's *lieben und arbeiten* (to love and to work).

The heterogeneity and absence of evidence to support treatment of individual personality disorders led researchers to largely ignore specific DSM Axis II personality disorder categories and adopt a more parsimonious approach to treatment, focusing instead on dimensions of psychopathology that cut across various personality disorders. The limitations of categorical models led to the development of a trait-based algorithm initially proposed by Siever and Davis (1991) and further developed by Soloff (1998). This new algorithm posited that four dimensions cutting across all personality disorder categories--affective instability, anxiety-inhibition, cognitive-perceptual disturbances, and impulsivity-aggression--should be studied rather than individual symptom clusters or diagnoses. This model has served as a dominant framework for understanding the evidence regarding the effects of medication on personality disorders (Bateman *et al.* 2015).

The diagnosis and classification of personality disorders are shifting toward a more dimensional model of classification (Widiger and Simonsen 2005). Although several models were proposed in DSM-IV-TR (American Psychiatric Association 2000), the model included in Section III of DSM-5 as an alternative to current categorical classifications is based on the empirically supported Five Factor Model, which includes the following broad domains: negative affectivity (vs. emotional stability), detachment (vs. extraversion), antagonism (vs. agreeableness), disinhibition (vs. conscientiousness), and psychoticism (vs. lucidity) (Widiger and Costa 1994). This model, in contrast to other models, was felt to adequately cover the full range of personality disorder symptomatology and has amassed the most empirical support (Widiger and Costa 1994). Compared with other models, it was felt to more accurately reflect normal as well as abnormal personality functioning and to better account for the symptoms and traits of DSM-IV-TR personality disorders (Clark 2007). The aspects of personality functioning considered to be most important to people across all cultures and languages when they describe themselves and others pertain to interpersonal relatedness, a domain thought to form the core of personality disorders (Pincus 2005) and captured by the two factors of extraversion and agreeableness.

Despite the formidable challenges in understanding what constitutes disordered personality features and their optimal treatment approach, reasons for optimism exist. The traditional view that personality disorders are necessarily chronic, stable over time, and marked by poor outcomes has been challenged in recent years in light of the fact that the more serious epiphenomena of disorders such as borderline personality disorder (BPD), including serious suicide attempts, impulsive behaviors, misuse of services, and aggressive outbursts, all show improvement with treatment. Findings from longitudinal studies of personality disorders such as the Collaborative Longitudinal Personality

Disorders Study and the McLean Study of Adult Development have challenged the traditional entrenched pessimism about the poor prognoses of personality disorders such as BPD (Gunderson *et al.* 2011; Zanarini *et al.* 2010). Such findings have driven the removal from DSM-5 of the separate Axis II category altogether as well as the introduction of terms such as *remission* and *relapse* to the conceptualization of personality disorders.

Pharmacotherapy for Cluster B Personality Disorders

Almost all of the clinical research trials examining medication treatments for personality disorders have studied BPD. The symptom clusters typically targeted in this condition, although varying from trial to trial in how they are defined and assessed, are dysregulated impulsivity and aggression, affective lability and hyperreactivity, cognitive-perceptual disorganization, anxiety, and dissociation. Dysregulation of impulses and affective instability are widely viewed as the hallmark symptoms of BPD. A retrospective chart review of 87 inpatients diagnosed with BPD between 2008 and 2012 found that 94% of all BPD inpatients received at least one psychotropic drug at the time of discharge. Overall prescription of psychotropic drugs was greater in this cohort compared with a 1996-2004 cohort (Timaus *et al.* 2019). Studies suggest that despite the limitations in our knowledge of treatments for BPD, drugs are very frequently prescribed, and polypharmacy is common, with antipsychotics, antidepressants, and mood stabilizers being the most commonly prescribed medication groups (Bridler *et al.* 2015; Knappich *et al.* 2014; Riffer *et al.* 2019; Zanarini *et al.* 2004b). One recent, rather selective review of randomized controlled trials testing drug treatments for BPD found a lack of sufficient evidence to support the use of pharmacological treatments for BPD (Stoffers-Winterling *et al.* 2020), although data from our review presented here suggest a more nuanced role for medications. Findings from this review did not support fluoxetine as a beneficial treatment option for the prevention of suicidal behavior in people with BPD. A real-world effectiveness study suggested that lamotrigine likewise is not a clinically effective treatment for BPD (Crawford *et al.* 2018). The review by Stoffers-Winterling *et al.* (2020) clearly indicated a need for more randomized controlled trials to evaluate the drugs, including atypical antipsychotics, that are most commonly used by people with BPD but also by people presenting with distinct comorbid conditions.

Conventional Antipsychotics

Abnormalities in dopamine signaling are thought to underlie the cognitive-perceptual symptoms of BPD, which include paranoia, perceptual aberrations, and subtle thought disorder, and this understanding forms the rationale for the use of antipsychotics to treat the disorder. BPD patients have been found to have higher plasma and cerebrospinal fluid levels of the dopamine metabolite homovanillic acid, and dopamine receptor genetic polymorphisms have been found to interact with traumatic attachment stressors to produce the attachment insecurity and disorganization thought to be integral to BPD (Steele and Siever 2010). On the whole, studies of conventional antipsychotics suggest significant improvements in anger with haloperidol and in suicidality with flupentixol decanoate, whereas effects on psychosis, irritability, and affective symptoms have been variable (Table 56-1). Any benefits of older antipsychotic agents must be weighed against these agents' well-established propensity to cause extrapyramidal symptoms and tardive dyskinesia.

TABLE 56-1. Summary of medication treatment trials with antipsychotics in borderline personality disorder (BPD)

Study	Subjects	Antipsychotic(s)	Other agent(s)	Duration	Outcome
Typical antipsychotics					
Leone 1982	80 BPD	Loxapine	Chlorpromazine	6 weeks	Improvement with both agents; greater improvement in depression and anger-hostility with loxapine
Montgomery and Montgomery 1982	30 BPD	Depot flupentixol	Placebo	4-6 months	Decrease in suicide attempts
Serban and Siegel 1984	16 BPD, 14 SztPD, 16 both	Thiothixene, haloperidol	--	12 weeks	Improvement in cognition, paranoia, anxiety, depression, social function with both agents (thiothixene > haloperidol)
Goldberg *et al.* 1986	17 BPD, 13 SztPD, 20 both	Thiothixene	Placebo	12 weeks	Decreased psychosis, anxiety
Soloff *et al.* 1986, 1989	35 BPD, 4 SztPD, 51 both	Haloperidol	Amitriptyline, placebo	5 weeks	Improvement in hostile depression, impulsivity, global functioning with haloperidol; improvement in depression but worsening on other measures with amitriptyline
Cowdry and Gardner 1988	16 BPD	Trifluoperazine	Alprazolam, carbamazepine, tranylcypromine, placebo	6-week crossover	Improvement but tolerability issues with trifluoperazine; greatest improvement on mood, anxiety, impulsivity with tranylcypromine; decreased severity of behavioral dyscontrol with carbamazepine; increased behavioral dyscontrol and suicidality with alprazolam
Soloff *et al.* 1993	42 BPD, 66 BPD and SztPD	Haloperidol	Phenelzine, placebo	5 weeks	Minimal improvement with haloperidol; improvement in depression, anxiety,

Note. SztPD = schizotypal personality disorder.

Study	Subjects	Antipsychotic(s)	Other agent(s)	Duration	Outcome
					anger, hostility with phenelzine
Cornelius *et al.* 1993	Continuation of Soloff *et al.* 1993 study			16-week extension	Reduced irritability but worsening of depression, leaden paralysis with haloperidol; modest improvement in depression and irritability with phenelzine
Atypical antipsychotics					
Frankenburg and Zanarini 1993	15 refractory BPD	Clozapine	--	2-9 months	33% overall improvement
Schulz *et al.* 1998	BPD	Risperidone	Placebo	8 weeks	Modest improvement, no better than placebo
Schulz *et al.* 1999	11 BPD (7 also SztPD)	Olanzapine	--	8 weeks	Generally modest to moderate improvement
Zanarini and Frankenburg 2001	28 BPD	Olanzapine	Placebo	6 months	Decreased anger, paranoia, anxiety, interpersonal sensitivity
Rocca *et al.* 2002	15 BPD with marked aggression	Risperidone	--	8 weeks	Decreased aggression, improved global functioning
Bogenschutz and Nurnberg 2004	40 BPD	Olanzapine	Placebo	12 weeks	Greater overall improvement in BPD severity
Villeneuve and Lemelin 2005	23 BPD	Quetiapine	--	12 weeks	Improved impulsivity, other measures, global function
Nickel *et al.* 2006	52 BPD	Aripiprazole	Placebo	12 weeks	Improvement on all outcome measures, including depression, anger, anxiety
Bellino *et al.* 2006	14 BPD	Quetiapine	--	12 weeks	Improvement especially in impulsiveness/aggressiven

Note. SztPD = schizotypal personality disorder.

Study	Subjects	Antipsychotic(s)	Other agent(s)	Duration	Outcome
					ess
Perrella *et al.* 2007	29 BPD	Quetiapine	--	12 weeks	Improvement especially in aggression and low mood
Schulz *et al.* 2007	314 BPD	Olanzapine	Placebo	12 weeks	No difference in overall symptom improvement between olanzapine and placebo groups
Zanarini *et al.* 2007	451 BPD	Low-dosage olanzapine (2.5 mg/day), moderate-dosage olanzapine (5-10 mg/day)	Placebo	12 weeks	Greater overall improvement for moderate-dosage olanzapine compared with low-dosage olanzapine and placebo
Linehan *et al.* 2008	24 BPD	Olanzapine	Placebo	6 months	Greater reductions in irritability and aggression with olanzapine
Pascual *et al.* 2008	60 BPD	Ziprasidone	Placebo	12 weeks	No difference in overall symptom improvement between groups
Zanarini *et al.* 2011	451 BPD	Olanzapine	Placebo	12 weeks	Significant reduction in overall BPD severity
Bellino *et al.* 2011	18 BPD	Paliperidone extended release	--	12 weeks	Significant reduction in overall BPD severity
Black *et al.* 2014	95 BPD	Quetiapine	Placebo	8 weeks	Significant reduction in overall BPD severity
Lee *et al.* 2016	95 BPD	Quetiapine	Placebo	8 weeks	Reduction in levels of overall psychological distress, interpersonal sensitivity, depression, hostility compared with placebo

Note. SztPD = schizotypal personality disorder.

Study	**Subjects**	**Antipsychotic(s)**	**Other agent(s)**	**Duration**	**Outcome**
Bozzatello *et al.* 2017	51 BPD	Asenapine	Olanzapine	12 weeks	Asenapine was found to be more effective than olanzapine at treating affective instability; olanzapine demonstrated better efficacy for treating paranoid ideation and dissociation
Rohde *et al.* 2018	25,916 BPD	Clozapine	--	2 years	Significant reduction in psychiatric admissions, psychiatric bed-days, number of patients with intentional self-harm or overdose

Note. SztPD = schizotypal personality disorder.

Atypical Antipsychotics

Atypical antipsychotics have received increased attention in recent years (see Table 56-1). On the whole, BPD treatment studies using atypical antipsychotics have shown improvements in affective instability, impulsivity, psychosis, and interpersonal dysfunction. In clinical practice, it appears that atypical antipsychotics are prescribed more frequently than conventional agents because of their greater tolerability and lower risks of extrapyramidal symptoms and tardive dyskinesia. A number of studies have examined olanzapine in the treatment of BPD (see Table 56-1). The largest study to date was conducted by Zanarini *et al.* (2011). In this 12-week randomized, double-blind, placebo-controlled trial, 451 outpatients with DSM-IV (American Psychiatric Association 1994) BPD received olanzapine 2.5 mg/day (*n* = 150), olanzapine 5-10 mg/day (*n* = 148), or placebo (*n* = 153). Olanzapine 5-10 mg/day showed a clinically modest advantage over placebo in the treatment of overall borderline psychopathology. Treatment-emergent adverse events included somnolence, fatigue, increased appetite, and weight gain (Zanarini *et al.* 2011). A 12-week open-label extension of the study found sustained improvements over longer durations (Zanarini *et al.* 2012).

Another large-scale placebo-controlled study comparing the efficacy and tolerability of low and moderate dosages of extended-release quetiapine in 95 adults with BPD found that participants in the low-dosage quetiapine (150 mg/day) group had significant improvement on measures of overall BPD severity compared with those in the placebo group (Black *et al.* 2014). Moreover, 82% in the low-dosage quetiapine group were rated as responders compared with 74% in the moderate-dosage (300 mg/day) group and 48% in the placebo group. Treatment-emergent adverse events included sedation, changes in appetite, and dry mouth. The overall completion rate for the 8-week double-blind treatment phase was 67% (67% for the low-dosage quetiapine group, 58% for the moderate-dosage quetiapine group, and 79% for the placebo group) (Black *et al.* 2014). Furthermore, an analysis of this study found that both low and moderate dosages of quetiapine were effective at reducing levels of overall psychological distress, interpersonal sensitivity, depression, and hostility compared with placebo (Lee *et al.* 2016).

A 2-year mirror-image study among 25,916 patients with BPD investigating the effects of clozapine showed that clozapine was associated with a significant reduction in psychiatric admissions per patient, from 2.52 to 2.00, and a significant reduction in psychiatric bed-days, from 190.08 to 65.95. The study also found that the number of patients with intentional self-harm or overdose decreased significantly, from 189 to 114, after clozapine initiation (Rohde *et al.* 2018). An open-label pilot study of asenapine versus olanzapine for the treatment of BPD found asenapine to be more effective than olanzapine in treating affective instability. Although olanzapine demonstrated better efficacy in treating paranoid ideation and dissociation, the study was underpowered to detect a difference between the two groups on the dissociation and paranoid ideation domain (Bozzatello *et al.* 2017).

Antidepressants

Although older antidepressant medications, including tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), have shown modest efficacy in improving affective symptoms of BPD (Cornelius *et al.* 1993; Cowdry and Gardner 1988; Soloff *et al.* 1993), both TCAs and MAOIs pose serious risks of overdose and have the potential for adverse events that are of particular concern in this unstable, impulsive population.

BPD studies with selective serotonin reuptake inhibitors (SSRIs) have yielded mixed findings. Whereas some older studies suggested statistically significant superiority of SSRIs over placebo in BPD (Coccaro and Kavoussi 1997; Markovitz 1995; Salzman *et al.* 1995), more recent controlled studies with SSRIs have shown either no difference from placebo or an additional benefit over placebo only when SSRIs are used to augment standard treatments such as dialectical behavior therapy (Simpson *et al.* 2004). SSRI monotherapy also demonstrated no statistical benefit over atypical antipsychotic monotherapy for depression and impulsive aggression (Zanarini *et al.* 2004a). Results from a Delphi study conducted by 18 international experts suggested a valuable role for SSRIs in the treatment of affective instability among older adults with BPD, with the first-choice SSRI being either sertraline or citalopram. The experts also agreed that SSRIs can be used as a second choice for treating impulsive behavior in this patient group (Schulkens *et al.* 2021). BPD studies with serotonin-norepinephrine reuptake inhibitors such as venlafaxine (Markovitz and Wagner 1995) and the newer agent duloxetine (Bellino *et al.* 2010) have also shown modest efficacy in treating affective symptoms (irritability, anger) and impulsive behaviors (self-injury), but these trials were limited by their open-label design and small sample sizes. Ketamine has recently received attention in the treatment of BPD because of its demonstrated efficacy in decreasing depression and suicidality in individuals with depression. Preliminary results from an ongoing trial of intravenous ketamine in BPD found that depression and suicidality decreased significantly in responders compared with nonresponders following treatment, although comparison of responders and nonresponders is not an optimal study design. Overall, the early results suggest that people with BPD may potentially respond to ketamine and that ketamine appears to be well

tolerated among this group (Null *et al.* 2019). Studies of antidepressant treatment of BPD are summarized in Table 56-2.

TABLE 56-2. Summary of medication treatment trials with antidepressants in borderline personality disorder (BPD)

Study	**Subjects**	**Antidepressant(s)**	**Other agent(s)**	**Duration**	**Outcome**
Soloff *et al.* 1986, 1989	35 BPD, 4 SztPD, 51 both	Amitriptyline	Haloperidol, placebo	5 weeks	Improvement in depression but worsening on other measures with amitriptyline; improvement in hostile depression, impulsivity, global functioning with haloperidol
Soloff *et al.* 1993	42 BPD, 66 BPD and SztPD	Phenelzine	Haloperidol, placebo	5 weeks	Improvement in depression, anxiety, anger, hostility with phenelzine; minimal improvements with haloperidol
Cornelius *et al.* 1993	Continuation of Soloff *et al.* 1993 study			16-week extension	Modest improvement in depression and irritability with phenelzine; reduced irritability but worsening of depression, leaden paralysis with haloperidol
Cowdry and Gardner 1988	16 BPD	Tranylcypromine	Alprazolam, carbamazepine, trifluoperazine, placebo	6-week crossover	Greatest improvement in mood, anxiety, impulsivity with tranylcypromine; decreased severity of behavioral dyscontrol with carbamazepine; increased behavioral dyscontrol and suicidality with alprazolam; improvement but tolerability issues with trifluoperazine
Markovitz *et al.* 1991	22 BPD or SztPD	Fluoxetine	--	12 weeks	Marked decline in self-mutilation, depression,

Note. SztPD = schizotypal personality disorder.

Study	Subjects	Antidepressant(s)	Other agent(s)	Duration	Outcome
					anxiety, interpersonal sensitivity, paranoia
Markovitz 1995	23 BPD	Sertraline	--	12 weeks	Half of subjects showed improvement in self-injury, anxiety, depression, suicidality
	Continuation of study			1 year	Decline in depression (56% of subjects) and self-injury (93%)
Kavoussi *et al.* 1994	9 personality disorder with impulsive aggression	Sertraline	--	8 weeks	Decreases in impulsive aggression
Markovitz 1995	17 BPD	Fluoxetine	Placebo	14 weeks	Global improvement on all measures
Salzman *et al.* 1995	27 BPD or BPD traits	Fluoxetine	Placebo	12 weeks	Decreases in anger, depression
Markovitz and Wagner 1995	45 BPD	Venlafaxine	--	12 weeks	40% global improvement, less self-injury
Coccaro and Kavoussi 1997	40 impulsive-aggressive personality disorder (one-third BPD), no major depressive disorder	Fluoxetine	Placebo	12 weeks	Marked decrease in aggression and irritability irrespective of changes in anxiety/depression
Rinne *et al.* 2002	38 BPD	Fluvoxamine	Placebo	6 weeks	Improvement in rapid mood shifts but not impulsivity or aggression
Simpson *et al.* 2004	20 BPD	Fluoxetine	Placebo	12 weeks	No significant additional benefit of adding fluoxetine to dialectical behavior therapy

Note. SztPD = schizotypal personality disorder.

Study	Subjects	Antidepressant(s)	Other agent(s)	Duration	Outcome
Zanarini *et al.* 2004a	45 BPD	Fluoxetine	Olanzapine, fluoxetine + olanzapine	8 weeks	Olanzapine and fluoxetine + olanzapine superior to fluoxetine monotherapy in reducing depression and impulsive aggression, but effect not statistically significant
Bellino *et al.* 2010	18 BPD	Duloxetine	--	12 weeks	Significant effects on impulsivity, anger, affective dysregulation

Note. SztPD = schizotypal personality disorder.

Mood Stabilizers

Mood stabilizers are known to calm excitatory neurotransmission, but the various agents differ in terms of their mechanism of action and effects on GABAergic and glutamatergic signaling mechanisms. As a class, mood stabilizers have gained increasing attention as a medication for the treatment of BPD symptoms, demonstrating moderate effect sizes on impulsive aggression, affective instability, self-injurious behaviors, and overall functioning.

Early studies supported a role for lithium in BPD (Rifkin *et al.* 1972). In a single small controlled study (Links *et al.* 1990), 17 subjects with BPD received 6 weeks each of lithium, the TCA desipramine, and placebo in a randomized crossover design, and 10 subjects completed at least two medication trials. Neither medication was better than placebo for depressive symptoms, although lithium led to a significant decrease in anger and suicidality according to clinician but not patient perception.

Anticonvulsants are used more widely than lithium in the treatment of BPD symptoms. Early studies with carbamazepine reported mixed findings, with some showing improvement in behavioral dyscontrol (Cowdry and Gardner 1988) and others showing no significant improvement with carbamazepine treatment (de la Fuente and Lotstra 1994) compared with placebo.

More recently, anticonvulsant studies have focused on valproate and newer anticonvulsants. In one placebo-controlled trial, 16 outpatients with BPD were treated for 10 weeks with valproate or placebo (Hollander *et al.* 2001). Global improvement was significant by two measures in patients treated with valproate, but the small sample size and high dropout rate precluded statistically significant findings. In another controlled study, valproate's efficacy was examined in 30 women with comorbid BPD and bipolar II disorder over 6 months of treatment (Frankenburg and Zanarini 2002). Valproate at an average dosage of 850 mg/day was well tolerated and resulted in significantly greater improvement in interpersonal sensitivity, hostility/anger, and aggression compared with placebo.

A larger placebo-controlled multicenter trial of valproate showed some efficacy for impulsive aggression in Cluster B personality disorders (Hollander *et al.* 2003). In this study, 91 outpatients selected for the presence of prominent impulsive aggression and the absence of bipolar I disorder or current major depressive disorder were randomly assigned to 12 weeks of treatment with placebo or valproate (mean dosage of 1,400 mg/day). Valproate was well tolerated overall, with only 17% of participants discontinuing because of valproate-related adverse events. The main finding of the study was a significant decrease in impulsive aggression in the last month of treatment, with valproate treatment reducing irritability, impulsive behaviors, and overall aggression, including verbal assault, assault against objects, and assault against others (Hollander *et al.* 2003).

Controlled studies have focused on lamotrigine (200 mg/day) and topiramate (200-250 mg/day) and suggest that both agents may offer therapeutic benefits in terms of treating affective instability and impulsivity in BPD. Lamotrigine (at a target dosage of 200 mg/day) demonstrated efficacy in treating impulsivity, affective symptoms, and aggression in BPD (Tritt *et al.* 2005). Long-term follow-up studies suggested that the benefits of lamotrigine are sustained and that it is an effective and relatively safe agent for longer-term treatment of aggression in women with BPD (Leiberich *et al.* 2008). However, results from a placebo-controlled randomized trial of lamotrigine in adults with BPD found no evidence to support the use of lamotrigine for treating the core symptoms of BPD (Crawford *et al.* 2018). Topiramate is another agent that has demonstrated efficacy for certain dimensions of BPD, such as anger (Loew *et al.* 2006; Nickel *et al.* 2004, 2005). Follow-up studies of topiramate support its efficacy long-term (Loew and Nickel 2008; Nickel *et al.* 2006). BPD treatment trials with mood stabilizers are summarized in Table 56-3.

TABLE 56-3. Summary of medication treatment trials with mood stabilizers in borderline personality disorder (BPD)

Study	Subjects	Mood stabilizer(s)	Other agent(s)	Duration	Outcome
Rifkin *et al.* 1972	21 emotionally unstable character disorder	Lithium	Placebo	6 weeks	Decreased mood lability
Cowdry and Gardner 1988	16 BPD	Carbamazepine	Trifluoperazine, tranylcypromine, alprazolam, placebo	6-week crossover	Decreased severity of behavioral dyscontrol with carbamazepine; greatest improvement in mood, anxiety, impulsivity with tranylcypromine; increased behavioral dyscontrol and suicidality with alprazolam; improvement but tolerability issues with trifluoperazine

Study	**Subjects**	**Mood stabilizer(s)**	**Other agent(s)**	**Duration**	**Outcome**
Links *et al.* 1990	17 BPD	Lithium	Desipramine, placebo	6-week crossover	No significant improvement in depression with lithium or desipramine; trend toward improvement in anger and suicidality (lithium > desipramine); clinician-rated overall improvement (lithium > desipramine)
de la Fuente and Lotstra 1994	20 BPD without depression	Carbamazepine	Placebo	4 weeks	No effect for depression, behavioral dyscontrol, global symptoms
Stein *et al.* 1995	11 BPD	Valproate	--	8 weeks	Modest benefit; half responders; less depression, anxiety, anger, impulsivity, rejection sensitivity
Pinto and Akiskal 1998	8 BPD without depression	Lamotrigine	--	1 year	Two discontinued; three robust global responders with decreased impulsivity and suicidality
Frankenburg and Zanarini 2002	30 BPD	Valproate	Placebo	6 months	Significant improvement in hostility, anger, aggression, interpersonal sensitivity
Hollander *et al.* 2001	16 BPD	Valproate	Placebo	12 weeks	Reduction in interpersonal problems, depression; some improvement in anger (not statistically significant)
Hollander *et al.* 2003	91 impulsive-aggressive Cluster B	Valproate	Placebo	12 weeks	Significant decrease in impulsive aggression

Study	Subjects	Mood stabilizer(s)	Other agent(s)	Duration	Outcome
Nickel *et al.* 2004	29 male BPD	Topiramate	Placebo	8 weeks	Decreased anger, significant weight loss
Nickel *et al.* 2005	42 male BPD	Topiramate	Placebo	8 weeks	Decreased anger, weight loss
Tritt *et al.* 2005	24 female BPD	Lamotrigine	Placebo	8 weeks	Decreased anger, no weight changes
Loew *et al.* 2006	56 female BPD	Topiramate	Placebo	10 weeks	Improvements in interpersonal sensitivity, anxiety, quality of life, weight loss
Crawford *et al.* 2018	20 BPD	Valproate extended release	--	12 weeks	Overall improvement, decreased irritability and aggression
Simeon *et al.* 2007	276 BPD	Lamotrigine	Placebo	52 weeks	Results suggest that treatment with lamotrigine is neither cost-effective nor clinically effective

Other Medications and Agents

Despite their widespread use, benzodiazepines on the whole are not recommended for use in the treatment of BPD because of their risk of worsening impulsivity and suicidality (Cowdry and Gardner 1988). Studies using the a_2-adrenergic agonist clonidine showed its efficacy in the treatment of comorbid PTSD and BPD (Ziegenhorn *et al.* 2009) and suggested a role for clonidine in the treatment of hyperarousal and sleep disturbances associated with BPD. Finally, several randomized controlled trials support the use of omega-3 fatty acids in reducing aggression and affective symptoms in patients with moderate to severe BPD (Zanarini and Frankenburg 2003).

Future Directions for Research, Including Neuropeptides and Other Agents

Drugs are routinely prescribed in clinical practice for the treatment of BPD, although no psychotropic medication has been FDA approved for this disorder. Although more controlled studies on these medications in BPD have become available in recent years, there is general agreement among the reviews in this field that the evidence is weak because of the severe methodological limitations of most studies. Small sample sizes, different gender proportions, heterogeneous selection criteria and assessment instruments, and high rates of dropout are the most relevant limitations. In addition, the mean duration of the trials is too short (32 days to 24 weeks) and insufficient to draw conclusions about the long-term efficacy and tolerability of medications in a long-lasting disorder such as BPD. For many drugs, most studies are open-label trials, which have limited clinical meaning because there is significant evidence of spontaneous changes in BPD symptoms over time. Current treatment guidelines diverge on the role of medications in BPD, which produces uncertainty among clinicians (Bozzatello *et al.* 2020).

Psychopharmacological research in patients with BPD has centered on neuropeptides, including opioids, oxytocin, vasopressin, and neuropeptide Y, all of which modulate complex networks of neurotransmitter systems and facilitate the coordination of affective signaling and behaviors. BPD has been conceptualized as being related to disturbed attachment, and thus oxytocin, vasopressin, and opioids may be of particular relevance for treating BPD, given the developmental role of these neuropeptides in attachment and the relationship between attachment security and stable social cognitive representations of self and other (Fonagy and Luyten 2009; Stanley and Siever 2010).

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In the past decade, a shift from a high predominance of prescribing antidepressants to the present-day preference for mood stabilizers and second-generation antipsychotics has been observed. Since 2010, no trials have been conducted in patients with BPD to assess the efficacy and tolerability of antidepressants. Recent systematic reviews have found insufficient evidence to support the prescribing of these drugs to BPD patients, except in the case of comorbidity with depression or anxiety disorders. In contrast, more recent controlled trials have indicated that mood stabilizers (valproate, topiramate, and lamotrigine) and second-and third-generation antipsychotics (olanzapine, quetiapine, and aripiprazole) can significantly affect core symptoms of BPD, such as impulsive-behavioral dyscontrol, affective instability, and cognitive-perceptual symptoms. First-generation antipsychotics have failed to demonstrate effects on BPD symptoms, except for reducing impulsive-aggressive behaviors during acute states, and adverse effects greatly limit these agents' use. Dietary omega-3 supplementation and oxytocin have garnered growing interest among researchers because of promising findings in terms of beneficial effects, in particular on the symptom domain of anger (Bozzatello *et al.* 2020).

Although some studies have suggested a role for opiate antagonists in the treatment of dissociative symptoms and flashbacks in BPD (Bohus *et al.* 1999; Griengl *et al.* 2001), other trials have not demonstrated any benefit of opioid antagonist treatment for acute symptoms of tension and dissociation in BPD (Philipsen *et al.* 2004).

Another neuropeptide system that has received increased attention for drug intervention in the treatment of interpersonal dysfunction is the oxytocin system. Oxytocin is associated with empathic processing and affiliative bonding and has been shown to have attenuating effects on the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Oxytocin deficits have been linked to attachment insecurity and separation distress, and oxytocin plays a role in the mediation of social cues, trust, and prosocial behavior (Bartz and Hollander 2006). Lower cerebrospinal fluid levels of oxytocin have been found in women with a history of childhood abuse or neglect (Heim *et al.* 2009), and early experimental studies suggested a role for the oxytocin system in attenuating emotional and hormonal responses to stress in BPD (Simeon *et al.* 2011).

Individuals with BPD have been found to lack psychophysiological and amygdala indicators of habituation to repeated interpersonal affective stimuli of positive or negative valence (Hazlett *et al.* 2012). Working through interpersonal experiences may be difficult for BPD patients, and adjunctive medication treatment that targets the capacity for habituation may optimize overall treatment efficacy. Habituation, a process dependent on neuroplasticity and changes in receptor density, is fundamentally affected by glutamatergic *N*-methyl-D-aspartate signaling, which suggests a role for glutamatergic medications in improving the affective, impulsive, interpersonal, and cognitive symptoms of BPD. Enhanced learning and psychophysiological habituation modulated by *N*-methyl-D-aspartate signaling could synergize psychopharmacology and psychotherapy, analogous to strategies proposed for PTSD with respect to enhancement of fear extinction and interference of traumatic memory consolidation (Grosjean and Tsai 2007; Ripoll 2013).

Endocannabinoid neurotransmission has been implicated in impulsivity (Pattij and Vanderschuren 2008), depression and suicidality (Vinod and Hungund 2006), and psychosis (Parolaro *et al.* 2010), possibly related to modulation in dopaminergic signaling (Fitzgerald *et al.* 2012). Both BPD and complex PTSD are powerfully associated with the experience of interpersonal violence during childhood and adolescence. These disorders frequently co-occur and often result in pervasive problems in emotion regulation and pain perception, processes that involve the endocannabinoid system. A study investigated serum levels of the endocannabinoids anandamide and 2-arachidonoylglycerol and related fatty acid ethanolamides in BPD patients, PTSD patients, and healthy control subjects. Significant alterations were found for both endocannabinoids in BPD and for the fatty acid ethanolamide oleoylethanolamide in PTSD, which suggests respective links to these disorders (Schaefer *et al.* 2014).

There is evidence that cyclical hormone changes (e.g., higher progesterone levels in the luteal phase, estrogen fluctuations at ovulation and in the luteal phase) may affect the expression of BPD features among at-risk women (Eisenlohr-Moul *et al.* 2015). Finally, altered levels of inflammatory cytokines such as interleukin-6 (Coccaro *et al.* 2015), prolactin (Atmaca *et al.* 2015b), *N*-acetylaspartate (Atmaca *et al.* 2015a), and cortisol (Rausch *et al.* 2015) have been linked with BPD and suggest putative neurobiochemical targets for future drug research.

An individualized, tailored pharmacotherapy for BPD with the fewest medications needed to target the prominent symptom clusters could improve relevant aspects of the clinical picture. However, no medication is indicated to treat the global psychopathology of this personality disorder. Polypharmacy is still common in clinical practice. It is not supported by data and should be avoided or strongly limited. At the moment, pharmacotherapy alone cannot manage a complex, severe, impairing condition such as BPD. Several core symptom domains, such as fears of abandonment, chronic feelings of emptiness, and identity disturbances, are refractory to pharmacotherapy. They could be the focus of specific psychotherapies or combined therapies. According to available findings, psychotherapy appropriately adapted for severe personality disorders or combined with selected mood stabilizers or new antipsychotics appears to be the most promising therapeutic tool for treating BPD patients (Bozzatello *et al.* 2020).

Conclusions and Treatment Guidelines for Cluster B Personality Disorders

In summary, several open and controlled pharmacological treatment trials of BPD have been conducted. Interpretation of the findings is somewhat complicated by the diversity of patient presentations at treatment entry, including inpatient or outpatient status; overall severity of baseline pathology; presence of comorbid personality disorders; presence or absence of major depressive disorder, including atypical symptoms; emphasis on varying symptomatology, such as psychoticism or impulsive aggression; and use of a wide range of outcome measures. In addition, some of the core features of the disorder, such as identity diffusion, interpersonal vicissitudes, and primitive defensive structure, were never examined, and therefore the assumption that these features are less responsive to medication has not been proven empirically. On the basis of the existent algorithms in the literature, modified according to the results of the latest medication trials, we propose a medication treatment approach for BPD (Table 56-4).

TABLE 56-4. **Psychopharmacological treatment guidelines for borderline personality disorder**

If the most prominent symptoms are depression, interpersonal sensitivity, and impulsivity and aggression:

1. Start with a selective serotonin reuptake inhibitor (SSRI) (or related antidepressant).
2. *If good response*, maintain.
   If partial response, add a mood stabilizer.
   If no response, switch to a different mood stabilizer.
3. *If significant residual anger, anxiety, or dyscontrol*, add an atypical antipsychotic.

If the most prominent symptoms are mood lability, impulsivity and aggression, and family history of bipolar spectrum:

1. Start with a mood stabilizer (valproate; carbamazepine or lithium as alternatives).
2. *If good response*, maintain.
   If partial response, add a second mood stabilizer.
   If no response, switch to a different mood stabilizer.
3. *If significant residual anger, anxiety, or dyscontrol*, add an atypical antipsychotic.

If the most prominent symptoms are paranoia, psychoticism, hostility, and overwhelming anxiety:

1. Start with an atypical antipsychotic (olanzapine and risperidone are the most studied).
2. *If good response*, maintain.
   If partial response, add an SSRI or mood stabilizer.
   If no response and minimal mood symptoms, switch to a typical antipsychotic.

In almost all Cluster B personality disorder trials, BPD has been the primary focus. Although some of these trials, mentioned individually in the overview above, included mixed samples of Cluster B participants, they did not present separate analyses for non-BPD diagnoses. Therefore, the general principle to follow in treating Cluster B disorders other than BPD would be to target symptom clusters with medications as per the guidelines developed for BPD (see Table 56-4). In general, narcissistic and histrionic personality disorders are not characterized by the severe mood lability or impulse dyscontrol seen in BPD, but for individuals in whom such features are more prominent or problematic, medication trials can be attempted.

In regard to antisocial personality disorder, the general treatment guideline is that individuals whose symptoms meet full criteria for the disorder are generally treatment noncompliant and nonresponsive. Although there have been a multitude of interventions tested in the past, an appropriate algorithm fails to exist today. Literature suggests that early treatment of conduct disorder in children is the least costly and most effective treatment for antisocial behavior (Frick 2016). Very few pharmacological studies have focused on patients with antisocial personality disorder (Coccaro 1993). Early trials suggested a role for lithium in reducing markers of antisocial behavior, including rule infractions and impulsive-aggressive behavior, among incarcerated males (Wickham and Reed 1987).

Studies of phenytoin 300 mg/day among prisoners and outpatients also showed some benefit for impulsive (but not premeditated) behaviors as well as reduced measures of anxiety and depression (Stanford *et al.* 2001). Finally, there is some evidence of benefit from nortriptyline (25-75 mg/day) and bromocriptine (15 mg/day) (Powell *et al.* 1995) in reducing alcohol abuse among individuals with antisocial personality disorder, a significant finding in light of the fact

that men with antisocial personality disorder have been found to be three to five times more likely than those without the disorder to abuse alcohol and illicit drugs (Robins and Price 1991).

More recently, a report on four antisocial personality disorder inpatients in a maximum-security facility found decreases in impulsivity, hostility, aggressiveness, irritability, and rage reactions with quetiapine treatment at dosages of 600-800 mg/day (Walker *et al.* 2003). In general, patients with BPD who have some antisocial traits are more responsive to medication treatment than are purely antisocial patients. Studies with the mood stabilizer valproate suggested that individuals with antisocial personality disorder were less responsive to the pharmacotherapy than were subjects with other Cluster B personality disorders (Hollander *et al.* 2003). It also has been found, however, that BPD patients are significantly more likely than antisocial personality disorder patients to have received adequate medication trials with anxiolytics and antidepressants (Zanarini *et al.* 1988).

Pharmacotherapy for Cluster A Personality Disorders

Despite the impact that a Cluster A personality disorder may have on an individual, limited research is available regarding the pharmacological treatment of this disorder. In general, patients with a Cluster A personality disorder tend to isolate and may not readily seek medical attention. Therefore, they may not be easily recruited into research studies (Koch *et al.* 2016). The main symptoms of Cluster A personality disorders--cognitive and perceptual distortions--are reminiscent of both the positive and negative symptoms of schizophrenia, and dopaminergic dysregulation has been postulated to underlie these symptoms (Siever and Davis 1991). Schizotypal personality disorder (SztPD) is by far the most extensively investigated disorder of the cluster in terms of biological underpinnings (Siever 1985; Siever *et al.* 1990), relation to DSM-IV Axis I as a schizophrenia spectrum disorder (Asarnow *et al.* 2001; Kendler *et al.* 1994), and pharmacological treatment trials. Similar to schizophrenia patients, patients with SztPD often demonstrate cognitive processing deficits, structural functioning abnormalities, and other physiological abnormalities (McClure *et al.* 2007). Some studies have reported greater preservation of frontal volume in patients with SztPD (Siever and Davis 2004) compared with patients with schizophrenia. Functional MRI data point to abnormal caudate volumes in SztPD patients with associated cognitive deficits in working memory, implicating striatum dysfunction, and associated abnormalities in cortical-subcortical circuits may play a key role in disorders of cognition and behavior such as SztPD (Levitt *et al.* 2004).

Serban and Siegel (1984) treated a sample of patients, one-third of whom had SztPD and one-third of whom had SztPD and BPD, with either thiothixene or haloperidol without placebo and found marked improvement in psychotic spectrum symptoms. Goldberg *et al.* (1986) treated a sample of outpatients with BPD and/or SztPD with thiothixene or placebo and found a significant improvement in psychotic symptoms with thiothixene that was more pronounced in the patients with SztPD. Soloff *et al.* (1986, 1989), in a sample containing a sizable proportion of patients with combined SztPD and BPD, found haloperidol to be superior to placebo in the treatment of schizotypal symptoms but failed to replicate this finding in a later study (Soloff *et al.* 1993), possibly because of the lower severity of symptoms in the later study.

Schulz *et al.* (1999) reported improvement in psychotic symptoms in a small group of patients who received olanzapine, most of whom had SztPD that was comorbid with BPD. There is one published randomized, placebo-controlled trial of an atypical antipsychotic (risperidone 0.25-2.0 mg/day) focusing exclusively on SztPD, and it found risperidone to be significantly more efficacious than placebo (Koenigsberg *et al.* 2003).

The evidence for the use of antidepressants in the treatment of SztPD symptoms is weak and at times contradictory, with only a few open-label studies demonstrating some improvement in impulsive aggression, self-injurious behaviors, and depressive and psychotic symptoms with the SSRI fluoxetine (Coccaro and Kavoussi 1997; Markovitz *et al.* 1991) and other studies showing detrimental effects (worsening of hostility and paranoia) with the TCA amitriptyline (Soloff *et al.* 1986, 1989).

Randomized controlled trials have shown improved cognitive performance on neuropsychological tasks with pergolide, a dopaminergic agonist active at both the dopamine D_1 and D_2 receptors (McClure *et al.* 2010), and the noradrenergic a_{2A} agonist guanfacine (McClure *et al.* 2007). Research on the neurobiological substrates of social cognitive dysfunction (empathic deficits, relational paranoia, and social isolation in SztPD) may provide future targets for pharmacotherapeutic intervention.

The use of olanzapine, risperidone, haloperidol, fluoxetine, and thiothixene has yielded beneficial results in patients with SztPD; however, treatment with such agents should be considered on a case-by-case basis. A single case series of treatment for paranoid personality disorder in Denmark found no conclusive results to guide future treatment recommendations beyond the tentative conclusion that an antipsychotic may be beneficial. Similarly, because of the complete lack of evidence for schizoid personality disorder, no recommendation for pharmacotherapy treatment can be offered at this time. In conclusion, most of the literature analyzed in this chapter presents theoretical ideas of what may constitute the neurobiological factors of personality and what treatments may address these aspects. Further research is needed to evaluate specific pharmacological treatment of the Cluster A personality disorders. At this time, treatment with pharmacological agents is based on theory rather than evidence (Koch *et al.* 2016).

Pharmacotherapy for Cluster C Personality Disorders

Anxiety and behavioral inhibition are the main symptoms that characterize individuals with Cluster C personality disorders, although the focus of the anxiety varies across disorders. The anxiety centers on social interaction in avoidant personality disorder, need for control of uncertainty in obsessive-compulsive personality disorder, and conflicts surrounding autonomy in dependent personality disorder.

Limited data suggest a role for the MAOI phenelzine (Deltito and Perugi 1986; Liebowitz *et al.* 1988) and the SSRI fluoxetine (Deltito and Stam 1989) in the treatment of avoidant personality disorder. However, in all of these studies, most, if not all, of

the avoidant subjects had comorbid DSM-III (American Psychiatric Association 1980) social phobia (DSM-5 social anxiety disorder), and the criteria used to differentiate the two conditions and their medication response were not clearly defined. In a more systematic approach, Reich *et al.* (1989)

openly treated 14 patients with DSM-III-R (American Psychiatric Association 1987) social phobia with alprazolam for 8 weeks at a mean daily dose of 3 mg and specifically measured treatment response in nine avoidant personality traits on the basis of DSM-III-R diagnostic criteria for avoidant personality disorder. Six of the nine avoidant traits showed significant improvement during treatment, correlating with a change in subjective anxiety and disability.

Greve and Adams (2002) reported anecdotal evidence for the anticonvulsant carbamazepine in the treatment of irritability and hostility associated with obsessive-compulsive personality disorder. Although overlap with OCD was suggested by previous findings of a familial spectrum of OCD and obsessive-compulsive personality disorder (Samuels *et al.* 2000) and the clinical observation that both disorders involve compulsive behaviors, more recent data are emerging that support the separation of the two as distinct clinical entities, differentiable on the basis of obsessions in OCD versus excessive capacity to delay reward in obsessive-compulsive personality disorder (Pinto *et al.* 2014).

Conclusion

In this chapter we reviewed the pharmacological treatment of personality disorders, providing a conceptual framework, highlighting methodological limitations, and summarizing medication treatment trials to date. Almost all of these trials have focused on symptom clusters, such as psychoticism, impulsivity, hostility/aggression, mood instability, and anxiety/inhibition. This focus is consistent with the growing conceptualization of personality disorders as syndromes of overlapping traits arising from a complex interaction between genetic determinants and developmental processes, influenced by adverse life events, with the primary manifestations of the disorders represented as difficulties with interpersonal relationships. The translation of current research into robust clinical recommendations for the treatment of personality disorders has been hampered by a number of methodological limitations, including the heterogeneity of study populations, selective attention to BPD, and diversity in outcome measures. Despite these limitations, there is sufficient evidence to suggest a role for medications as an adjunctive treatment for symptom reduction, functional improvement, and overall adaptation for personality disorders. Progress in our understanding of the neurobiological underpinnings of personality and their component dimensions will help guide the development of better models of personality and its disordered forms, thereby providing a basis for rational pharmacotherapy to complement psychosocial interventions.

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CHAPTER 57

Treatment of Eating Disorders

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Anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED) have a combined prevalence of 3%-6%, given the diagnostic changes in DSM-5 (American Psychiatric Association 2013; Hudson *et al.* 2007; Mond 2013). About 10% of all cases of AN and BN are in males, with the proportion rising to about 30% for BED in clinical samples. Because much comorbid psychopathology is associated with each of these disorders, including current major depressive disorder in about 25% of cases, the treatment plan must take such disorders into account. At this point only two medications are approved by the FDA for the treatment of eating disorders: fluoxetine for BN and lisdexamfetamine (LDX) for BED. There are no approved medications for the treatment of AN.

Because there are several evidence-based psychotherapies for BN and BED, it is important to consider the relative efficacy of medication and psychotherapy in these disorders and whether adding either one to the other is effective. Hence, in the last section on each disorder I review this issue.

Bulimia Nervosa

BN usually begins in adolescence or early adulthood, with a prodromal period characterized by dissatisfaction with body shape and a fear of becoming overweight, followed by dietary restriction and weight loss.

Sooner or later, periods of dietary restriction are followed by episodes of binge eating experienced as a loss of control over food intake. Ultimately, the individual discovers purging, usually in the form of self-induced vomiting, with or without laxative or diuretic use, excessive exercise, or (less commonly) fasting, and in rare cases in the form of chewing food and spitting it out. Medical complications of BN include potassium depletion and other electrolyte disturbances, which combined with low weight may lead to cardiovascular complications and death (Gibson *et al.* 2019; Westmoreland *et al.* 2016). Other complications include esophageal bleeding, dental caries, salivary gland enlargement, and exercise injuries. Some 20% of patients with BN have a history of AN.

Antidepressants

Fluoxetine

Three seminal studies outlined the short-, medium-, and long-term effectiveness of fluoxetine. In a placebo-controlled trial 387 women with BN were randomly assigned to either fluoxetine (20 mg/day or 60 mg/day) or placebo for 8 weeks following a 1-week placebo washout (Fluoxetine Bulimia Nervosa Collaborative Study Group 1992). A dosage of 60 mg/day was found to be significantly more effective than either 20 mg/day or placebo in reducing binge eating and purging, with 20 mg/day showing an intermediate effect and being superior to placebo in reducing purging but not binge eating. A modest but statistically significant difference in weight loss was seen between women taking fluoxetine 60 mg/day (1.6 kg/day) and those taking placebo (0.0 kg/day). Indices of eating disorder psychopathology, such as body dissatisfaction, also improved at the 60 mg/day dosage. In a different study, 16 weeks in duration, 398 subjects with BN were randomly assigned to either fluoxetine 60 mg/day or placebo (Goldstein *et al.* 1995). A larger percentage of women in the fluoxetine group than in the placebo group reduced their vomiting by more than 50%

(53.1% vs. 35%). The difference for stopping vomiting was also statistically significant between the fluoxetine and placebo groups (19% vs. 12%).

Little is known about the long-term effectiveness of fluoxetine. In a study of this issue, 147 women with BN who had decreased their vomiting by at least 50% while taking 60 mg/day of fluoxetine over an 8-week period were randomly allocated to continue medication or to be switched to placebo (Romano *et al.* 2002). A survival analysis found that the group receiving active medication experienced a longer time to relapse than did the placebo group. Estimated relapse rates for the fluoxetine group at 3, 6, and 12 months were 19%, 29%, and 33%. It should be noted, however, that at the 12-month follow-up, 83% of the fluoxetine group and 92% of the placebo group had relapsed or dropped out. Side effects were reported at higher rates by those receiving fluoxetine compared with placebo. Side effects in these trials were insomnia, nausea, dizziness, sweating, and decreased libido. Hence, the safety profile is similar to that found in the treatment of depression.

Other Antidepressants

Fluoxetine should be the pharmacological agent of choice for the treatment of BN. However, most antidepressants, used off-label, appear to be effective at antidepressant dosages. Little is known about longer-term outcomes with antidepressants other than fluoxetine. One study compared different lengths of desipramine treatment for BN. Participants with BN treated for 16 weeks relapsed to pretreatment levels of binge eating when desipramine was withdrawn. However, those treated for 24 weeks maintained remission after withdrawal and at 1-year follow-up (Agras *et al.* 1992, 1994). This study suggests that patients who respond to antidepressant treatment should be given a minimum trial of 6 months on medication.

An interesting study involving 77 BN patients (Walsh *et al.* 2006b) examined the rate of decline in symptoms of bulimia with desipramine. The authors found that patients unlikely to respond to the antidepressant could be reliably identified after 2 weeks of treatment. This finding was replicated in a combined dataset ($N = 785$) from two controlled trials (Sysko *et al.* 2010). Patients who did not reduce binge eating or vomiting by 60% by week 2 of treatment were unlikely to respond to fluoxetine. Early identification of poor responders allows for the deployment of different approaches to treatment, for example, a different antidepressant or cognitive-behavioral therapy (CBT). Side effects and reasons for discontinuing the various medications are similar to those observed in the treatment of depression. However, a study of bupropion found that a higher-than-expected proportion of patients with bulimia developed grand mal seizures (Horne *et al.* 1988). The authors concluded that bupropion should not be used for the treatment of BN.

Anticonvulsants

Topiramate

The rationale for considering topiramate as a treatment for BN is that patients with epilepsy were found to experience appetite reduction and weight loss on this medication. In one study (Hoopes *et al.* 2003), patients whose symptoms met criteria for DSM-IV-TR BN (American Psychiatric Association 2000) were allocated at random to treatment with either topiramate ($n = 35$) or placebo ($n = 34$) over a 10-week period. Twenty-two (63%) of those in the topiramate group completed the trial, and topiramate was statistically superior at reducing binge eating and purging, with 22% of completers in remission at the end of treatment. Other studies have shown similar findings, with greater efficacy of topiramate over placebo in percent reductions in binge eating and purging, reductions in body dissatisfaction and drive for thinness, and reductions in anxiety and depression (Hedges *et al.* 2003; Nickel *et al.* 2005). The mean dose of topiramate in these studies was 100 mg/day (range 25-400 mg/day). Side effects commonly seen with topiramate are drowsiness, fatigue, distractibility, insomnia, and cognitive blunting.

Combined Treatment

CBT for BN developed in parallel with the use of antidepressants. On the basis of the research literature, CBT is considered the first-line treatment for BN because it appears to be more effective than antidepressant medication and other psychotherapies such as interpersonal psychotherapy (Linardon *et al.* 2017; National Institute for Health and Care Excellence 2017; Slade *et al.* 2018). The existence of two different and effective treatments, antidepressant medications and CBT, naturally led to the question of whether the combination of these treatments would be more effective than either treatment alone. A meta-analysis of controlled studies examining this question (Reas and Grilo 2021) found no advantage for combining treatments in 10 of 12 studies. Hence, in the absence of patient preference for medication over psychotherapy, CBT should be the treatment of choice for BN, followed by medication if there is a poor response to psychotherapy.

Binge-Eating Disorder

The principal features of BED are episodes of binge eating followed by marked distress. Purging and other compensatory behaviors do not occur in this condition, although about 10% of patients with BED have a history of BN.

Between 1% and 3% of women in the general population have symptoms that meet criteria for BED. The ratio of women to men with BED is approximately 3:2, the highest rate for men of any eating disorder. Although obesity is not a requirement for a diagnosis of BED, there is a substantial overlap between BED and obesity. Studies have shown that about one-quarter of obese individuals have symptoms that meet criteria for BED and that the prevalence of binge eating increases as BMI increases (Marcus *et al.* 1985; Spitzer *et al.* 1993; Telch *et al.* 1988). Moreover, BED is associated with comorbid psychopathology similar to that seen in BN.

Lisdexamfetamine

LDX, a prodrug that has L-lysine conjugated to dextroamphetamine, is FDA approved for the treatment of ADHD in both children and adults and was approved in 2015 for the treatment of moderate to severe BED in adults (Bello and Yeomans 2018). Commonly reported side effects include dry mouth, decreased appetite, insomnia, and headache. Because LDX is converted to amphetamine, it has addictive potential; hence, the U.S. Drug Enforcement Agency has classified LDX as a Schedule II controlled medication. Patients with BED should be carefully screened for past drug or alcohol overuse.

A series of randomized double-blind, controlled studies demonstrated the safety and efficacy of LDX in both the short and longer term, clarified dosage levels, and investigated the course of improvement in binge eating. In the first study, 514 adults whose symptoms met criteria for BED were randomly allocated to dosages of 30 mg/day, 50 mg/day, or 70 mg/day or to placebo for 11 weeks (McElroy *et al.* 2015). The primary outcome, change in the number of binge-eating days per week, significantly favored LDX over placebo except for the 30 mg/day dosage, with no difference between the two higher dosages. Cessation of binge eating over a 4-week period occurred in 21.3% of participants in the placebo group compared with 34.9% of individuals receiving LDX at 30 mg/day, 42.2% at 50 mg/day, and 50% at 70 mg/day. Weight loss was 0.1 kg in the placebo group compared with 4.3 kg across all three dosages of LDX. There were no serious adverse events.

Following this pivotal study, two parallel randomized, placebo-controlled studies enrolled a total of 386 participants whose symptoms met criteria for BED (McElroy *et al.* 2016). Each study included multiple sites (50 and 43). The dosage of LDX, either 50 mg/day or 70 mg/day, was optimized for each participant depending on tolerability for a duration of 12 weeks. In both studies, those randomly allocated to LDX reduced their binge eating and weight significantly more than those in the placebo groups. Abstinence rates for the two studies combined were 13.6% for the placebo groups and 38.1% for the LDX groups. The results were similar in both studies, replicating the results of the previous Phase II study. McElroy *et al.* (2017) further examined the rate of improvement in binge eating at weekly intervals in the placebo and LDX groups. The frequency of binge eating, abstinence from binge eating, and percent change in body weight differed between placebo and LDX after 1 week of treatment and continued to increase, stabilizing around week 9. Hence, there is a rapid therapeutic response to LDX both for reduction in and cessation of binge eating and for weight loss.

A multinational, multisite study further examined the longer-term effectiveness of LDX (Hudson *et al.* 2017). A total of 411 participants whose symptoms met criteria for BED began open-label treatment with LDX. The dosage of LDX was individually optimized

for each participant at either 50 mg/day or 70 mg/day. At the end of 12 weeks on LDX, 275 participants who remained in the study and who binged once or less per week were randomly allocated to placebo or to LDX to examine the rate of relapse over a 6-month period. Relapse was defined as > 2 binge-eating episodes a week for 2 consecutive weeks. In the primary analysis, the time to relapse was significantly longer in the LDX group than in the placebo group, with 5.1% of participants in the LDX group relapsing compared with 34.4% in the placebo group. Only 20% of those receiving LDX in the randomized phase did not complete the study.

Antidepressants

Double-blind, placebo-controlled studies suggest that antidepressants are at least as useful in the treatment of BED as they are in the treatment of BN. Early placebo-controlled studies found desipramine to be effective in reducing binge eating, with an abstinence rate of 60% (McCann and Agras 1990). Studies of selective serotonin reuptake inhibitors have suggested moderate efficacy, with overall remission rates of approximately 40% compared with 20% for placebo (Appolinario and McElroy 2004; McElroy *et al.* 2010). Most studies showed some degree of weight loss, which for the most part was not clinically significant.

Anticonvulsants

Topiramate

Anticonvulsants such as topiramate also appear useful in the treatment of BED (McElroy *et al.* 2009). The mechanism of action of anticonvulsants in BED is unclear but is likely a combination of appetite suppression and satiety enhancement via delayed gastric emptying. A 16-week double-blind multisite study in which 394 participants with BED were allocated at random to receive either topiramate or placebo provided evidence for the efficacy of topiramate (McElroy *et al.* 2007). The median dosage of topiramate was 300 mg/day. Dropout rates were equivalent between the groups (29% topiramate, 30% placebo). Fifty-eight percent of participants in the topiramate group and 29% of those in the placebo group were in remission at the end of the study period. There was a mean weight loss of 4.5 kg in the topiramate group versus a small weight gain in the placebo group. The most common side effects specific to topiramate were paresthesia and difficulty concentrating. Hence, topiramate leads to a reasonable rate of remission of the eating disorder combined with substantial and clinically meaningful weight loss.

Medication Combinations

Phentermine/Topiramate

The combination of phentermine and topiramate was approved by the FDA for the treatment of obesity in 2012. The rationale for combining the two medications was to increase both effectiveness and tolerability. The improved tolerability may be due to the opposing side effects of the two medications. The stimulant effects of phentermine may reduce the sedative and cognitive effects of topiramate, leading to greater tolerability and reduced dropout rates. Lower dosages of each medication may also reduce side effects. Only one study of the combination for treating an eating disorder

has been reported to date. Using a crossover design, Safer *et al.* (2020) compared the combination of phentermine and topiramate with placebo in

22 participants (18 whose symptoms met DSM-5 criteria for BED and 4 whose symptoms met criteria for BN). Abstinence rates (no binge eating in a 4-week period) were 63.6% for the combined medication and 9.1% for placebo, with a weight loss of 6.5 kg in the medication group compared with a slight gain in weight for the placebo group, rates roughly comparable to those obtained in studies of LDX. These results suggest that the combination of phentermine and topiramate is likely to be effective in the treatment of BED. No serious adverse effects were noted in this study, and cardiovascular effects in the medication and placebo groups were comparable. The combination of phentermine and topiramate appears promising and merits further larger-scale studies.

Naltrexone/Bupropion

Although there is clear evidence that the combination of naltrexone and bupropion leads to significant weight loss in the treatment of obesity, there has been only one small-scale controlled study of the effectiveness of this combination in treating BED (Grilo *et al.* 2021). Twenty-two participants were randomly allocated to receive either a fixed daily dosage of a combination medication (naltrexone 50 mg, bupropion extended release 300 mg) or placebo for 12 weeks with a 6-month follow-up. Naltrexone/bupropion was well tolerated, and there were substantial reductions from baseline in binge eating and eating disorder psychopathology, but there were no significant differences in clinical outcomes between patients receiving the medication and patients receiving placebo. Weight reductions favored the naltrexone/bupropion combination. Larger trials of this combination are needed.

Combined Treatment Modalities

BED presents three problems to the clinician: binge eating; overweight; and comorbid psychopathology, in particular depression and anxiety disorders. Hence, comprehensive treatment should address all of these problems. CBT is widely regarded as the treatment of choice for BED (National Institute for Health and Care Excellence 2017), followed by interpersonal psychotherapy, although weight loss is minimal with either psychotherapy; hence, it may be necessary to use medication to treat the residual overweight. Among the medications available for the treatment of obesity, the largest mean weight losses (minus placebo response) have been for naltrexone/bupropion (6.1 kg), phentermine (6.4 kg), and phentermine/topiramate (8.7 kg) (Dragano *et al.* 2020). There are few direct comparisons of psychotherapy and medication for the treatment of BED. In a meta-analysis of treatments aimed at reducing binge eating compared with placebo or no treatment, there was an advantage for CBT (RR = 4.95) compared with LDX (RR = 2.61). However, there has been no direct comparison of LDX and CBT or of their combination. For patients who prefer medication, current evidence suggests that LDX is the most effective pharmacological agent reducing both binge eating and weight.

Anorexia Nervosa

AN is characterized by dietary restriction followed by marked weight loss, intense fear of gaining weight, and disturbance in the experience of body shape (e.g., feeling fat despite marked weight loss). It is the most lethal psychiatric disorder. A meta-analysis of 41 cohorts from peer-reviewed studies published between 1966 and 2010 found that AN patients were 5.2 times more likely to die prematurely than females in the general population and 18.1 times more likely to die by suicide (Keshaviah *et al.* 2014). Because of the disabling nature and chronicity of the condition and the lack of evidence-based treatments for the persistent form of the disorder early identification and treatment of the disorder are essential.

Controlled pharmacological studies in both adolescents and adults with AN have generally shown a lack of efficacy (Blanchet *et al.* 2019; Suarez-Pinilla *et al.* 2015). However, many of the studies are underpowered or have very high dropout rates, which makes it difficult to draw firm conclusions regarding effectiveness.

Antipsychotics

Most studies of antipsychotic agents in the treatment of AN, including chlorpromazine, pimozide, sulpiride, olanzapine, and risperidone, have shown no evidence of efficacy for weight gain (Blanchet *et al.* 2019). However, in a multisite trial 152 outpatients with AN were randomly assigned to olanzapine or placebo for 16 weeks (Attia *et al.* 2019). The primary outcomes were rate of weight gain and obsessionality, with secondary outcomes of improvement in eating disorder and other psychopathology. Almost half the participants had dropped out by week 16, with no difference between the two randomized groups. However, those receiving olanzapine gained weight more rapidly than those receiving placebo, with a medium effect size of 0.63. There were no differences between the two groups for obsessionality, anxiety, or eating disorder psychopathology. Olanzapine was well tolerated, with no difference in rates of medication discontinuation between medication and placebo. The results of this study suggest that the use of olanzapine by patients with AN confers a modest benefit for weight gain. The authors suggested that olanzapine may be a useful adjunct to psychological treatment.

Antidepressants

There is little evidence that antidepressants are effective when used in either an inpatient treatment setting focusing on weight gain or an outpatient setting focusing on weight maintenance (Blanchet *et al.* 2019; Mitchell *et al.* 2013). An inpatient study found that fluoxetine was not effective in hospitalized patients with AN (Attia *et al.* 1998). In that study, 31 women hospitalized with AN participated in a 7-week randomized, double-blind, placebo-controlled trial of fluoxetine at a mean dosage of 56 mg/day. Four patients in the fluoxetine group and four patients in the placebo group terminated the trial early. Although all patients in the study showed improvement, no significant differences were seen between those who received active medication and those who received placebo. In addition, there was no apparent effect of medication on depression or on symptoms of obsession. This study suggests that fluoxetine has no effect over and above that of an inpatient program and adds to the consistent failure in the literature to show a beneficial effect of antidepressant medication during the period of weight regain.

Despite promising findings in an earlier small-scale outpatient study (Kaye *et al.* 2001), a double-blind, placebo-controlled trial of 93 adult outpatients found no benefit for fluoxetine in either promoting weight maintenance or prolonging time to relapse (Walsh *et al.* 2006a). As is usual in this population, a large proportion of patients

dropped out or terminated treatment early (51% of fluoxetine-treated and 63% of placebo-treated patients). A fairly high proportion of patients were dissatisfied with treatment. Hence, the use of fluoxetine is not indicated in the treatment of AN except to treat comorbid psychopathology.

Combined Treatment

There is no evidence-based psychotherapeutic treatment for persistent AN; CBT, psychodynamic psychotherapy, and medical care plus supportive psychotherapy are all effective in producing modest weight gain, but there is little evidence that one treatment is either superior or specific (Wonderlich *et al.* 2020). Hence, no psychotherapy has specific effects in the treatment of persistent AN, and there is no evidence that combining psychotherapy and medication is effective.

A specific family therapy for adolescents with AN (family-based treatment) that helps parents take charge of their child's eating is effective in both the short and long term, with about 50% of adolescent patients with anorexia recovered both at the end of treatment and at follow-up (Lock 2019). Moreover, it is more effective than other psychotherapies with which it has been compared. No pharmacological agent has shown benefit for this group of patients; therefore, for adolescent AN, family therapy in general and family-based treatment in particular are the only evidence-based treatments (Hay *et al.* 2014; Resmark *et al.* 2019).

Conclusion

It is perhaps surprising that there are so few effective pharmacological agents for the treatment of eating disorders. The place of psychopharmacological agents in the treatment of BN has been well worked out. Treatment with sequential trials of different antidepressants should result in abstinence rates of about 40%. The addition of CBT enhances the effectiveness of antidepressants. The most effective pharmacological agent for the treatment of BED appears to be LDX because it effectively reduces both binge eating and weight. In the case of AN, there is now evidence from one controlled trial that olanzapine may be helpful for weight gain. No other pharmacological agents are helpful in either inpatient or outpatient treatment of adult patients except to treat comorbid psychiatric disorders. There is insufficient information regarding adolescent AN to provide guidance regarding the use of medication at this point.

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CHAPTER 58

Treatment of Insomnia

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Disturbances of sleep occur at some point in the life of essentially everyone. However, the presence of a clinically significant insomnia disorder requires that the sleep disturbance meet a specific set of criteria: 1) There is a complaint of difficulty falling asleep or staying asleep, 2) this complaint is associated with clinically significant distress and/or daytime functional impairment, 3) these difficulties occur despite an adequate opportunity for sleep, and 4) the sleep disturbance is present for three or more nights per week for at least 3 months (American Academy of Sleep Medicine 2014; American Psychiatric Association 2013; Krystal 2007).

Available research suggests that insomnia disorder has a population prevalence of approximately 10% and is associated with impairments in quality of life; accidents; falls in elderly people; limitations of function; increased risk of hypertension; and increased risk of major depressive disorder, anxiety disorders, suicidality, and substance-related disorders (Avidan *et al.* 2005; Baglioni *et al.* 2011; Bathgate *et al.* 2016; Breslau *et al.* 1996; Ford and Kamerow 1989; Harvey 2008; Johnson *et al.* 2000; Kessler *et al.* 2012; Koski *et al.* 1998; Leger *et al.* 2008; Morin *et al.* 2011; Ohayon 2002; Ohayon and Reynolds 2009; Roth *et al.* 2011; Stone *et al.* 2014; Vgontzas *et al.* 2013; Winsper and Tang 2014). Insomnia disorder most often occurs along with psychiatric and medical conditions (Ford and Kamerow 1989; Sarsour *et al.* 2010). For many years, insomnia, especially when chronic, was assumed to be a symptom of these conditions (National Institutes of Health 1984, 2005). On this basis, directing treatment specifically to chronic insomnia was discouraged. Instead, it was recommended that treatment be administered for the associated medical and psychiatric conditions under the assumption that the insomnia would improve along with the other symptoms of the medical or psychiatric condition (National Institutes of Health 1984, 2005). Over time, the accumulating evidence suggested that this model was fundamentally flawed (Krystal 2015; National Institutes of Health 2005). In approximately 15% of the patients with insomnia who have so-called primary insomnia, no associated condition exists to treat (Edinger *et al.* 2011; Ohayon 1997). Evidence also indicates that treating the associated medical or psychiatric condition often fails to alleviate the insomnia and that insomnia has an adverse effect on the treatment response and course of depression, pain conditions, and anxiety disorders (Krystal 2015; Krystal *et al.* 2012; National Institutes of Health 2005). Further undermining the model that insomnia is invariably a symptom of psychiatric and medical conditions are the data referred to earlier indicating that insomnia is a risk factor for subsequent suicidality and psychiatric and medical conditions (Avidan *et al.* 2005; Baglioni *et al.* 2011; Bathgate *et al.* 2016; Breslau *et al.* 1996; Ford and Kamerow 1989; Harvey 2008; Johnson *et al.* 2000; Kessler *et al.* 2012; Koski *et al.* 1998; Stone *et al.* 2014; Vgontzas *et al.* 2013; Winsper and Tang 2014). These observations have led to a change in the paradigm for insomnia treatment.

It is now appreciated that the relationship between insomnia and associated conditions is complex and often bidirectional and that directing treatment specifically to insomnia is generally warranted whether that insomnia occurs on its own or as a condition comorbid with psychiatric or medical conditions (National Institutes of Health 2005). Two primary types of treatment are available for specifically targeting insomnia disorder: 1) cognitive-behavioral therapy for insomnia, the primary nonpharmacological therapy for insomnia; and 2) pharmacological therapy. A large evidence base supports the efficacy of cognitive-behavioral therapy for insomnia for the treatment of insomnia, including primary insomnia and insomnia occurring with pain and major depressive disorder (Carney et al. 2017; Edinger et al. 2001, 2005; Manber et al. 2016; Morin et al. 2006; National Institutes of Health 2005). Pharmacotherapy, the focus of this chapter, is by far the most commonly administered treatment for insomnia disorder.

In this chapter, I review the neuropharmacology of pharmacological therapies for insomnia and examine their characteristics and clinical application. This information will optimize medication management for insomnia.

Sleep-Wake Pharmacology-- The Basis for Understanding Pharmacological Treatments for Insomnia

The pharmacological systems that regulate sleep-wake function consist of two types: 1) systems that promote sleep and 2) systems that promote wakefulness (Saper *et al.* 2005) (Table 58-1). These systems are mutually inhibitory, such that greater activity in sleep-promoting systems inhibits the wakefulness-promoting systems and vice versa, thereby stabilizing the state of an individual into either sleep or wakefulness. The most important sleep-promoting systems include GABA, galanin, adenosine, and melatonin, whereas the wake-promoting systems include histamine, acetylcholine, norepinephrine, serotonin, dopamine, and hypocretin/orexin (Saper *et al.* 2005). Agents that have therapeutic effects in treating insomnia either enhance the activity of one or more sleep-promoting systems or block the effects of one or more wake-promoting systems (Krystal *et al.* 2013b).

TABLE 58-1. Sleep-wake neurotransmitters (sleep-promoting and wake-promoting)

Key sleep-promoting systems	Key wake-promoting systems
g-Aminobutyric acid	Hypocretin/orexin
Galanin	Norepinephrine
Melatonin	Histamine
	Acetylcholine
	Serotonin
	Dopamine

Although there have long been agents available that differ in which of the sleep-wake systems they affect, it has generally been believed that the pharmacological

mechanism of action of agents used to treat insomnia has no bearing on their clinical effects (Krystal *et al.* 2013b). Instead, clinical effects have been assumed to be determined by dosage and pharmacokinetics (Krystal *et al.* 2013b). The higher the dosage, the greater the clinical sleep-enhancing effect; the higher the dosage and the more rapid the absorption, the sooner the clinical effect occurs; and the higher the dosage and the longer the elimination half-life, the longer the duration of sleep enhancement (Krystal *et al.* 2013b). This model emerged at the time when the pharmacological management of insomnia was dominated by a group of agents--benzodiazepines (e.g., triazolam, temazepam, flurazepam) and nonbenzodiazepines (e.g., zolpidem, zaleplon, eszopiclone)--that had a common mechanism: sleep enhancement via positive allosteric modulation of GABA_A receptors (Krystal 2009; Krystal *et al.* 2013b). Systematic data on clinical effects were essentially available only for these agents, for which the pharmacokinetics/dosage model was largely correct. Their peak effect occurs at the time of peak blood level, the speed of onset of clinical effects is proportional to the rate of absorption, and the duration of effects is proportional to the elimination half-life. However, medications are available for the treatment of insomnia that have a fundamentally different mechanism and specifically block a single wake-promoting system (Krystal *et al.* 2013b). These agents with targeted, less global effects carry the promise of an improved risk-benefit ratio when used by patients with sleep problems that are especially responsive to a particular agent's mechanistic effects. Studies examining the clinical effects of these more targeted medications have only relatively recently been conducted, and they have verified these agents' improved risk-benefit profiles. Their findings have also begun to undermine the prevailing model, in which clinical effects are posited to be driven solely by dosage and pharmacokinetics, with mechanism of action playing no role (Herring *et al.* 2016; Krystal *et al.* 2010, 2011; Michelson *et al.* 2014).

One agent that illustrates this point is doxepin, a highly selective histamine type 1 (H1) receptor antagonist that (at a dose of 3-6 mg) enhances sleep by specifically blocking the wake-promoting effects of histamine (Krystal *et al.* 2010, 2011, 2013b). The peak therapeutic effect does not occur at peak blood level, which is approximately 3-4 hours after ingestion, but instead occurs at the end of the night about 4 hours later (Krystal *et al.* 2010, 2011, 2013b). According to the model in which pharmacokinetics and dosage dominate clinical effects, this would not be possible, and a drug with a peak effect at the end of the night would be useless because it would cause prohibitive morning sedation or impairment (Krystal *et al.* 2013b). Because clinical effects should be proportional to blood level, and blood level only decreases incrementally over time, a drug with its biggest effect in hour 8 of an 8-hour night should have effects that are nearly as large in hour 9, the first hour of the day, at which time sleep-enhancing effects are problematic (Krystal *et al.* 2013b). Yet doxepin 3-6 mg has its greatest effects in hour 8 without clinically significant effects during waking 1 hour later (Krystal *et al.* 2010, 2011). This profile of effects is incompatible with a model in which therapeutic effects are dominated by pharmacokinetic factors and indicates that factors other than pharmacokinetics play an important role in determining clinical effects (Krystal *et al.* 2013b). These factors include the specific properties of the pharmacological system(s) modulated by a given drug and activity in other systems that can affect sleep-wake function, which are determined by factors such as time of day, the behavior of the individual taking the medication, and the psychosocial context (e.g., stress, a novel environment, excitement [Krystal *et al.* 2013b]). The relevance of other systems was not apparent during the era when GABA$_A$-positive allosteric modulators dominated insomnia pharmacotherapy, because those agents broadly inhibit brain function, nonspecifically shutting down all of the wake-promoting systems. Agents that specifically inhibit a single wake-promoting system have brought to light how activity in systems that are not inhibited can contribute to clinical effects.

Consider again doxepin 3-6 mg as an example. The clinical effects of specifically blocking the histamine system reflect both the characteristics of the histamine system and the activity in parallel wake-promoting systems. Histamine is under the control of the circadian clock, and its release varies systematically over the 24-hour cycle (Krystal *et al.* 2013b). When its release is minimal, the clinical effects of blocking H$_1$ receptors should be minimal, whereas at times of significant release of histamine, a therapeutic effect can be expected. However, the activity of other sleep-wake-modulating systems that are not inhibited by doxepin 3-6 mg also plays a role. Whether the blockade of H$_1$ receptors manifests in a clinical sleep-enhancing effect will depend on the activity in other wake-promoting systems. If this activity is high, those systems will themselves sustain wakefulness even with significant blockade of H$_1$ receptors (Krystal *et al.* 2013b).

The activity in these parallel wake-promoting systems can be dependent on psychosocial context; for example, in an individual who is stressed or excited, noradrenergic neuronal activity is likely to be high and could maintain wakefulness despite H$_1$ receptor antagonism (Krystal *et al.* 2013b). Another example concerns the effects of time of day. After an individual awakens for the day during the usual waking period, activity in the neuropeptide hypocretin/orexin system is increased and can maintain wakefulness even if H$_1$ receptors are blocked (Krystal *et al.* 2013b). This explains why doxepin 3-6 mg might have its largest effects in hour 8 of an 8-hour night and not have impairing effects after waking: at the end of the night, histamine release is high, and the parallel wake-promoting activity is normally relatively minimal, yet after waking, activity in parallel wake-promoting systems increases and can maintain wakefulness despite the blockade of H$_1$ receptors (Krystal *et al.* 2013b). Thus, to determine the likely clinical effects of a medication, it is necessary to know not only dosage and pharmacokinetic parameters but also the mechanism of action in terms of which pharmacological system(s) it modulates, whether that system is modulated by the circadian rhythm and state (e.g., activity, stress, novelty), and what the circadian and state dependence are of the parallel pharmacological systems that could oppose or enhance clinical effects.

Accordingly, the model that is the basis for the current chapter is that mechanism matters and that three primary factors determine the clinical effects of medications used to treat insomnia: 1) the mechanism of action, 2) drug pharmacokinetics, and 3) dosage. I review the characteristics of the various medications available for the treatment of insomnia organized by pharmacological mechanism of action. This includes reviews of the important drugs that enhance sleep-promoting systems, which consist of benzodiazepines, nonbenzodiazepines, and melatonin receptor agonists, and the important wake-promoting system antagonists, which consist of selective antihistamines, selective hypocretin/orexin receptor antagonists, selective adrenergic receptor antagonists, and nonselective wake-promoting system antagonists.

Pharmacological Treatments for Insomnia

Agents That Improve Sleep by Enhancing Sleep-Promoting Systems

The appendix table at the end of this chapter provides an overview of the properties of medications commonly used to treat insomnia.

$GABA_A$-Positive Allosteric Modulators

Benzodiazepines. Benzodiazepines are a group of medications that are $GABA_A$-positive allosteric modulators and share a chemical structure (Krystal 2009; Minkel and Krystal 2013). The site on the $GABA_A$ receptor complex to which these agents bind is referred to as the *benzodiazepine binding site*. By binding to this site, these agents broadly enhance GABA-mediated inhibition, which inhibits all of the wake-promoting systems and promotes sleep (Sieghart and Sperk 2002).

Benzodiazepines used for the treatment of insomnia. Five agents are indicated for the treatment of insomnia by the FDA: triazolam, flurazepam, temazepam, estazolam, and quazepam (Krystal 2009). Several other agents--clonazepam, alprazolam, and lorazepam--are commonly used to treat insomnia but have approved indications for conditions other than insomnia, such as anxiety and seizures (Krystal 2009).

Clinical therapeutic effects as indicated by available studies. Triazolam, flurazepam, estazolam, quazepam, and temazepam were found to have efficacy for the treatment of both sleep-onset problems and sleep-maintenance difficulty in at least one placebo-controlled trial (Krystal 2009).

Effects on systems other than sleep-wake systems. GABA is the predominant inhibitory neurotransmitter in the brain. For this reason, benzodiazepines, which broadly enhance $GABA_A$-mediated inhibition, can affect many brain systems. Some of the associated effects, including anxiety reduction, myorelaxant, and antiseizure effects, can be therapeutic for some patients (Krystal 2009). Other associated effects represent adverse effects, including cognitive impairment, motor impairment, and abuse potential (Krystal 2009).

Optimal target patient population. Benzodiazepines are best suited for use by those who can benefit from the effects these agents may have on systems other than sleep-wake systems, including those with anxiety or pain problems. Compared with other available agents, these agents also have relatively potent beneficial effects for sleep-onset problems (Krystal 2009). Thus, although the adverse effects of these medications outweigh the beneficial effects for most patients, for some with sleep-onset problems and comorbid conditions, these medications may have the best risk-benefit ratio of the available agents.

Nonbenzodiazepines. The term *nonbenzodiazepine* has been used to describe a set of agents that work by the same mechanism as benzodiazepines, positive allosteric modulation of $GABA_A$ receptors, but do not have the chemical structure of benzodiazepines (Krystal 2009; Minkel and Krystal 2013).

Nonbenzodiazepines used for the treatment of insomnia. Three agents are indicated for the treatment of insomnia by the FDA: zolpidem, zaleplon, and eszopiclone (Krystal 2009). Zolpidem is also available in formulations other than an immediate-release formulation, including an extended-release version and a transoral version that is absorbed through the oral mucosa to a degree.

Clinical therapeutic effects as indicated by available studies. Zolpidem, zaleplon, and eszopiclone were found to have efficacy for the treatment of sleep-onset problems in at least one placebo-controlled trial (Krystal 2009). However, only eszopiclone and the extended-release formulation of zolpidem have been found to have therapeutic effects for sleep-maintenance problems (Krystal *et al.* 2003, 2008a; Walsh *et al.* 2007). Both zaleplon and the transoral formulation of zolpidem have been found to have therapeutic effects for helping people return to sleep after middle-of-the-night awakenings (Roth *et al.* 2013; Zammit *et al.* 2006).

Effects on systems other than sleep-wake systems. Because nonbenzodiazepines are GABA$_A$ allosteric modulators like benzodiazepines, they have the potential to have broad inhibitory effects on brain function. However, some evidence indicates that the clinical effects of nonbenzodiazepines are more limited than those of benzodiazepines (Jia *et al.* 2009; Sanna *et al.* 2002). The clinical effects of benzodiazepines are believed to be mediated by their binding to four types of GABA$_A$ receptors, whereas nonbenzodiazepines bind less broadly to these GABA$_A$ receptors (Jia *et al.* 2009; Sanna *et al.* 2002). Zolpidem and zaleplon bind relatively specifically to GABA$_A$ receptors that are sleep-promoting and are also associated with cognitive and motor impairment, whereas eszopiclone tends to bind to GABA$_A$ receptors that are also associated with sleep enhancement and some degree of psychomotor impairment but have relatively greater myorelaxant, anxiolytic, and possibly antidepressant effects. Clinical evidence for this is that unlike zolpidem, eszopiclone has been found to lead to improvement in anxiety, depression, and pain when combined with the usual therapies for these conditions in placebo-controlled trials (Fava *et al.* 2006, 2009, 2011; Goforth *et al.* 2014; Krystal *et al.* 2007a; Pollack *et al.* 2008).

Optimal target patient population. Nonbenzodiazepines are among the most widely administered insomnia therapies because of their strong effects on sleep onset and the perception that they have a better safety profile than benzodiazepines. In general, nonbenzodiazepines are the treatments of choice for pharmacotherapy of sleep-onset problems. Zolpidem (modified release) and eszopiclone are also agents to consider along with hypocretin/orexin antagonists (see the subsection "Selective Hypocretin/Orexin Receptor Antagonists") for treating problems with sleep maintenance when they co-occur with sleep-onset problems; however, when sleep-maintenance problems occur without sleep-onset difficulty, selective H$_1$ receptor antagonists appear to have a more favorable risk-benefit profile (see "Selective H$_1$ Receptor Antagonists"). Individuals who have intermittent problems with waking up in the middle of the night who are appropriate candidates for using an as-needed rescue medication to help speed the return to sleep are best treated with transoral zolpidem and zaleplon on the basis of available data (Roth *et al.* 2013; Zammit *et al.* 2006). Finally, because only eszopiclone has been found to improve anxiety, depression, and pain outcomes when administered along with the usual first-line treatments for these conditions when they co-occur with insomnia, this medication should be considered as a first-line therapy for patients with insomnia occurring with these conditions (Fava *et al.* 2006, 2009, 2011; Goforth *et al.* 2014; Krystal *et al.* 2007a; Pollack *et al.* 2008).

Melatonin Receptor Agonists

Melatonin receptor agonists have melatonin receptor agonism as their primary clinical effect.

Melatonin receptor agonists used for the treatment of insomnia. Two selective melatonin receptor agonists are available: melatonin, which is available over the counter; and ramelteon, which is available by prescription only and is FDA approved for the treatment of insomnia (Krystal 2009).

Melatonin is released by the pineal gland during the dark period of the circadian cycle (Dubocovich *et al.* 2003). Sleep enhancement is believed to occur via agonist effects at membrane-bound G protein-coupled melatonin type 1 (MT$_1$) receptors, which inhibit the activity of neurons in the suprachiasmatic nucleus of the hypothalamus, the main circadian pacemaker (Dubocovich *et al.* 2003). Melatonin also binds to G protein-coupled melatonin type 2 (MT$_2$) receptors, which are also located on suprachiasmatic nucleus neurons and induce shifts in the phase of the circadian cycle (Dubocovich *et al.* 2003).

Ramelteon is a highly specific MT$_1$ and MT$_2$ agonist (Krystal 2009). It is substantially more potent than melatonin in affecting these receptors. It has an FDA indication for the treatment of sleep-onset insomnia only.

Clinical therapeutic effects as indicated by available studies. A sizable set of studies that have used a variety of dosages, formulations, and timings of dosing have been carried out to assess the effects of melatonin on individuals with sleep difficulty (Buscemi *et al.* 2005; Ferracioli-Oda *et al.* 2013). These studies indicate that melatonin seems to be associated with a modest improvement in sleep latency in insomnia patients. Whether the degree of improvement associated with melatonin use is sufficient to be perceived as beneficial by many insomnia patients remains unclear (Morin *et al.* 2015). Furthermore, the optimal dosage of melatonin for the treatment of insomnia has yet to be established. The strongest empirical support for the use of melatonin in treating insomnia is for its effects in improving sleep difficulties co-occurring with autism or other neurodevelopmental disorders (Niederhofer *et al.* 2003; Wirojanan *et al.* 2009).

Ramelteon has been shown in several placebo-controlled trials to have therapeutic effects only on sleep-onset difficulties (Krystal 2009).

Safety profile. Melatonin has highly selective effects on melatonin receptors, and as a result it has an excellent safety profile (Wilson *et al.* 2010). However, as mentioned earlier, the effects on MT_2 and melatonin type 3 (MT_3) receptors can affect physiology, although by far the most important clinical effect mediated by MT_2 and MT_3 binding is MT_2-mediated shifts in circadian rhythm (Dubocovich *et al.* 2003). This is believed to be responsible for the observation that melatonin is associated with greater therapeutic effects in those with delayed sleep phase syndrome, in which the circadian sleep-wake cycle is shifted forward, than in insomnia patients (Buscemi *et al.* 2005; Ferracioli-Oda *et al.* 2013).

Like melatonin, ramelteon has an excellent safety profile as a result of having pharmacological effects that are limited to melatonin receptors (Krystal 2009). It does not have abuse potential and is safe in those with sleep apnea and chronic obstructive pulmonary disease (Kryger *et al.* 2007, 2009).

Optimal target patient population. The available data indicate that melatonin should be considered as a first-line therapy for patients with insomnia occurring with autism and other neurodevelopmental problems as well as for those with insomnia occurring in the setting of circadian rhythm disorders (Buscemi *et al.* 2005; Ferracioli-Oda *et al.* 2013; Niederhofer *et al.* 2003; Wirojanan *et al.* 2009). In addition, melatonin can be considered for use by those with insomnia affecting only sleep onset.

Because ramelteon has effects only on sleep-onset difficulties, its use should be limited to those with only sleep-onset difficulties. It is especially well suited for use by those with obstructive sleep apnea and chronic obstructive pulmonary disease who have sleep-onset problems. It should also be considered for treating sleep-onset problems occurring in the setting of substance abuse or in individuals prone to substance abuse, but no studies have established its utility for this purpose.

Agents That Improve Sleep by Blocking Wake-Promoting Systems

Selective Histamine 1 Receptor Antagonists

Selective H_1 receptor antagonists promote sleep by blocking the arousing effects of histamine through antagonism of the H_1 receptor (Krystal *et al.* 2013b). The only highly selective H_1 receptor antagonist available is doxepin 3-6 mg. Doxepin was originally developed for the treatment of depression and is FDA approved for the treatment of depression and anxiety in dosages of 75-300 mg/day. In this dosage range, doxepin has clinically significant antagonism of adrenergic, serotonergic, and cholinergic receptors and the serotonin and norepinephrine transporters in addition to H_1 receptor antagonism (Krystal *et al.* 2013b). However, because H_1 receptor antagonism is by far doxepin's most potent effect, at low enough dosages this agent can have clinically significant effects only at H_1 receptors. The available evidence suggests that in the 3-to 6-mg range, doxepin is a highly selective H_1 receptor antagonist (Krystal *et al.* 2013b).

Available data from placebo-controlled trials carried out with doxepin 3 mg and 6 mg doses provided the first information about the clinical effects of selective wake-promoting

system antagonism and, as discussed earlier, indicated that they differ from the clinical effects of $GABA_A$ allosteric modulators (Krystal *et al.* 2013b). In addition to dosage and pharmacokinetics, which essentially determine the clinical effects of those other agents, the clinical effects of doxepin are dependent on factors such as time of day and the state of the patient (e.g., activity, stress, novelty) (Krystal *et al.* 2010, 2011, 2013b). This dependence of clinical effects on factors other than dosage and pharmacokinetics exists for all selective wake-promoting system antagonists and therefore represents a new paradigm for understanding the clinical effects of insomnia medications. As discussed earlier, the dependence of clinical effects of selective antagonists on factors other than dosage and pharmacokinetics reflects the fact that 1) the activity in the targeted wake-promoting systems is dependent on factors such as time of day and the state of the patient, and this will affect the degree of clinical effect occurring with antagonism; and 2) each wake-promoting system functions in parallel with other wake-promoting systems that are not blocked by selective antagonism, and the activity in these systems is also affected by factors such as time of day and patient state (Krystal *et al.* 2013b). The reason this is not the case for $GABA_A$ allosteric modulators is that they broadly inhibit all of the wake-promoting systems, and the clinical effects of enhancing $GABA_A$ activity are relatively less dependent on time of day and patient state (Krystal *et al.* 2013b).

Selective H_1 receptor antagonists used for the treatment of insomnia. Many medications that have H_1 receptor antagonist effects are currently available and used to treat insomnia (Krystal *et al.* 2013b). However, the only highly selective H_1 receptor antagonist currently used in the treatment of insomnia is doxepin in 3-and 6-mg/day dosages. It is approved by the FDA for the treatment of insomnia with an indication only for treating problems staying asleep.

Clinical therapeutic effects as indicated by available studies. The clinical trials carried out with doxepin 3 mg and 6 mg indicate that this medication has consistent therapeutic effects on sleep maintenance, in particular in the last third of the night, without consistent therapeutic effects on sleep-onset problems (Krystal *et al.* 2010, 2011, 2013b). Notably, the largest effect size appears not at peak blood level (3-4 hours after dosing) but in the last hour of an 8-hour night. As discussed earlier, this could not occur with a $GABA_A$ allosteric modulator without prohibitive morning impairment. It is hypothesized that the reason the therapeutic effects are greatest at the end of the night is that the activity of histamine neurons is relatively high during this period, whereas the activity in the parallel wake-promoting systems is relatively low (Krystal *et al.* 2013b). However, after waking, the activity in the histamine system may increase further, and the activity in parallel wake-promoting systems increases, thereby sustaining normal waking function despite significant H_1 blockade (Krystal *et al.* 2013b).

Effects on systems other than sleep-wake systems. Given the relatively greater potency of doxepin for H_1 receptors over other receptors, it should be possible in theory to find a dosage for each individual that causes clinically significant H_1 receptor antagonist effects and no effects on any other pharmacological systems. The observed clinical effects indicate that the 3-and 6-mg/day dosages achieve this type of selectivity for many individuals (Krystal *et al.* 2010, 2011). However, for some individuals,

these dosages may have effects other than H_1 receptor antagonism. When this is the case, the special advantages of highly selective antagonism are lost, and individuals may experience morning sedation and other adverse effects, including anticholinergic (e.g., dry mouth, constipation, blurred vision) and antiadrenergic (e.g., orthostatic hypotension) symptoms.

Optimal target patient population. Because of the pharmacological selectivity of doxepin 3 mg and 6 mg, it can have an improved risk-benefit profile over other agents when used to treat the type of problem that it specifically addresses: sleep-maintenance problems, in particular problems staying asleep at the end of the night (Krystal *et al.* 2013b). For this reason, doxepin 3-6 mg should be the treatment of choice for those individuals with difficulties staying asleep, in particular toward the end of the night, who do not have problems falling asleep. The lack of abuse potential suggests that this medication might be particularly useful in abuse-prone individuals with sleep-maintenance problems. The fact that H_1 receptor antagonism is the key mechanism of anti-allergy effects also suggests that this medication should be among the treatments of choice for sleep difficulties occurring with significant allergy symptoms.

Selective Hypocretin/Orexin Receptor Antagonists.

Hypocretin and orexin are both names given to the peptides released by neurons located in the lateral hypothalamus that are among the most important factors maintaining wakefulness (Krystal *et al.* 2013a; Sakurai

2014). The wake-promoting effects of these peptides are mediated by their binding to two receptors referred to as OX_1 and OX_2 (Sakurai 2014). Selective hypocretin/orexin receptor antagonists enhance sleep by blocking OX_1 receptors, OX_2 receptors, or both. The tremendous specificity of this effect is illustrated by the fact that there are only 10,000-20,000 hypocretin/orexin-releasing neurons in the entire brain (Sakurai 2014). This specificity enables drugs that block OX_1 and OX_2 receptors to promote sleep while having limited effects on other brain functions. However, because hypocretin/orexin neurons modulate activity in many brain areas, these agents would be expected to have some effects on functions other than sleep. Nonetheless, the relative lack of effect on areas of the brain mediating cognitive and motor function suggests that these agents may lack many of the adverse effects that have been associated with benzodiazepines and nonbenzodiazepines.

Selective hypocretin/orexin receptor antagonists used for the treatment of insomnia. There are three hypocretin/orexin receptor antagonists currently available for clinical use--suvorexant, lemborexant, and daridorexant--all of which are dual orexin (OX_1 and OX_2) receptor antagonists (DORAs) (Dauvilliers *et al.* 2020; Herring *et al.* 2016; Karppa *et al.* 2020; Michelson *et al.* 2014; Yardley *et al.* 2021; Zammit *et al.* 2020). The FDA granted these agents approval for the treatment of insomnia, with indications for treating sleep-onset and sleep-maintenance difficulties for all of them.

Clinical therapeutic effects as indicated by available studies. The clinical effects of suvorexant, lemborexant, and daridorexant have been documented in large-scale placebo-controlled trials (Dauvilliers *et al.* 2020; Herring *et al.* 2016; Karppa *et al.* 2020; Michelson *et al.* 2014; Mignot *et al.* 2022; Yardley *et al.* 2021; Zammit *et al.* 2020). These studies indicate that all of these medications have therapeutic effects on sleep onset and sleep maintenance, consistent with their FDA indications. However, relatively limited data are available for the FDA-approved dosage of suvorexant 10-20 mg (Herring *et al.* 2016).

Effects on systems other than sleep-wake systems. DORAs have minimal effects on systems other than the hypocretin/orexin system. As a result, the primary adverse effects of these agents are relatively limited and due to decreased hypocretin/orexin-mediated function. The primary such effect is daytime sedation or fatigue (Dauvilliers *et al.* 2020; Herring *et al.* 2016; Karppa *et al.* 2020; Michelson *et al.* 2014; Mignot *et al.* 2022; Yardley *et al.* 2021; Zammit *et al.* 2020).

Optimal target patient population. DORAs are among the agents that could be considered for first-line use in patients with problems both falling and staying asleep. An additional target population is insomnia patients with mild to moderate chronic obstructive pulmonary disease or obstructive sleep apnea because of evidence that these drugs do not exacerbate these conditions (Boof *et al.* 2022; Cheng *et al.* 2020; Sun *et al.* 2015, 2016). The amygdala, lateral septum, periaqueductal gray, and parabrachial nucleus have important projections to hypocretin/orexin neurons, which are believed to mediate stress-or anxiety-associated increases in arousal; thus, DORAs should in theory be particularly useful for patients with sleep problems occurring in the setting of stress or anxiety (Krystal *et al.* 2013a; Scammell and Winrow 2011). DORAs would also be expected to be particularly helpful for those trying to sleep at a time of day that is not their circadian sleep period on the basis of evidence that hypocretin/orexin neurons are the prime mediators of maintenance of sustained wakefulness during the usual circadian wake period (Krystal *et al.* 2013a; Zeitzer *et al.* 2020). However, additional studies are needed to determine whether these theoretical optimal target patient populations are actually best treated with DORAs.

Selective Alpha-1 Adrenergic Receptor Antagonists

Medications that are selective a_1-adrenergic receptor antagonists have long been available by prescription for the treatment of hypertension and benign prostatic hypertrophy. These agents include prazosin, silodosin, doxazosin, tamsulosin, alfuzosin, and terazosin. They may have sleep-enhancing effects by blocking the wake-promoting effects of norepinephrine, one of the important wake-promoting systems (Krystal and Davidson 2007; Krystal *et al.* 2013b; Saper *et al.* 2005). These drugs do this by blocking a_1-adrenergic receptors, which are primarily excitatory postsynaptic receptors. These agents have long been of interest for modulating anxiety (Charney and Redmond 1983). A sizable literature indicates that agents that dampen central noradrenergic neuronal activity or blunt noradrenergic system-mediated activation, such as a_1-adrenergic receptor antagonists, have clinical anxiolytic effects. Within this context, selective a_1-adrenergic receptor antagonists have found application in the treatment of sleep difficulties.

Because of their selectivity for a_1 receptors, these agents, like DORAs and selective H_1 antagonists, have the potential to improve sleep difficulties in patients with anxiety-related difficulties without causing many of the adverse effects that have limited the use of benzodiazepines and nonbenzodiazepines. A series of studies documented the therapeutic effects of prazosin on sleep difficulties in patients with PTSD (Goddard *et al.* 2010; Raskind *et al.* 2003, 2007, 2013; Taylor *et al.* 2008). However, more recently,

the largest studies conducted to date cast uncertainty on this picture because no significant effects of prazosin versus placebo were found on PTSD-associated nightmares and sleep disturbance (Raskind *et al.* 2018).

Selective a_1-adrenergic receptor antagonists used for the treatment of insomnia. Although several selective a_1-adrenergic receptor antagonists are available, the only one that has been studied extensively and used to any significant extent for treating sleep problems is prazosin (Goddard *et al.* 2010; Krystal and Davidson 2007; Raskind *et al.* 2003, 2007, 2013, 2018; Taylor *et al.* 2008). However, no selective a_1-adrenergic receptor antagonists have an FDA indication for treating insomnia.

Clinical therapeutic effects as indicated by available studies. The available studies, with the notable exception of the largest one, suggest that prazosin may improve sleep-maintenance difficulties and nightmares in patients with PTSD (Goddard *et al.* 2010; Krystal and Davidson 2007; Raskind *et al.* 2003, 2007, 2013, 2018; Taylor *et al.* 2008). Studies of the effects of this agent on primary insomnia or insomnia occurring with conditions other than PTSD have not been carried out.

Effects on systems other than sleep-wake systems. Prazosin has minimal effects on systems other than the noradrenergic system. As a result, the primary adverse effects of this agent are relatively limited and consist of orthostatic hypotension and associated dizziness (Goddard *et al.* 2010; Raskind *et al.* 2003, 2007, 2013; Taylor *et al.* 2008). Dry mouth, sweating, nasal congestion, and sedation also have been reported to occur.

Optimal target patient population. Prazosin can be considered for patients with sleep difficulties occurring in the setting of PTSD. Although studies are lacking, the use of this agent in treating sleep problems in patients with other anxiety disorders is of great interest. It also should be noted that prazosin is the only medication shown to have significant therapeutic effects on nightmares in those with and without PTSD. As a result, when the physician is faced with the need to treat nightmares in a patient who does not have PTSD, a trial of prazosin could be considered.

Nonselective Wake-Promoting System Antagonists

Some agents that were originally developed for the treatment of allergies are generally referred to as *antihistamines* because they all have significant H_1 receptor antagonism. However, none of these agents are particularly potent or selective H_1 receptor antagonists, and all have clinically significant effects on pharmacological systems other than the histamine system (Krystal *et al.* 2013b). Notably, agents such as doxepin and mirtazapine are more potent and selective H_1 receptor antagonists than any of these antihistamines, but they were never referred to by this name because they were originally developed for the treatment of depression and not allergies. As a result, they are generally referred to as *antidepressants*. Thus, it is important to appreciate that the terms *antihistamine* and *antidepressant* are more a reflection of the original targeted disorder than an indicator of drug pharmacology. A more appropriate term for these agents would be *nonselective antihistamines* or, for those with relatively broad pharmacological effects, *nonselective wake-promoting system antagonists*.

Nonselective antihistamines used for the treatment of insomnia. The nonselective antihistamines primarily used for the treatment of insomnia include agents that are available in many over-the-counter sleep treatments: diphenhydramine and doxylamine (Krystal *et al.* 2013b). They all have significant muscarinic cholinergic receptor antagonism in addition to H_1 receptor antagonism, and some have other important pharmacological effects (Krystal *et al.* 2013b). There is reason to believe that these nonhistaminergic effects influence both clinical effects on sleep problems and the side-effect profiles of these agents (Krystal *et al.* 2013b). Nonselective antihistamines promote sleep primarily by blocking the arousing effects of both histamine and acetylcholine.

Clinical therapeutic effects as indicated by available studies. Remarkably little systematic research has been carried out on the sleep effects of nonselective antihistamines considering how frequently these agents are used to treat sleep difficulties. Only two placebo-controlled trials have been completed (Glass *et al.* 2008; Morin *et al.* 2005). One, a crossover study that included 20 older adults with primary insomnia, indicated that diphenhydramine 50 mg decreased the number of awakenings compared with placebo but had no other significant effects on sleep problems (Glass *et al.* 2008). The other study evaluated diphenhydramine 25 mg in 120 adults with relatively mild insomnia and found that this medication led to significant improvement in self-reported sleep efficiency (time asleep/time in bed) but not in polysomnographic sleep efficiency or self-reported or polysomnographic sleep-onset latency or total sleep time (Morin *et al.* 2005).

Effects on systems other than sleep-wake systems. The adverse effects of nonselective antihistamines include, in addition to daytime sedation, dry mouth, dizziness, constipation, and blurred vision (Glass *et al.* 2008; Krystal *et al.* 2013b; Morin *et al.* 2005). Cholinergic receptor antagonism also increases the risk for urinary retention, memory impairment, and delirium, in particular in older individuals.

Optimal target patient population. The limited available data do not make a strong case for the utility of nonselective antihistamines. However, to the extent that they have therapeutic effects, these agents appear to be limited to improvements in sleep maintenance and not sleep onset (Glass *et al.* 2008; Morin *et al.* 2005). Thus, use should be limited to those without sleep-onset difficulty who have problems with sleep maintenance. The H_1 and cholinergic receptor antagonism of the agents suggests that they would be best suited for use by individuals experiencing sleep problems related to allergies or those with nasal congestion.

Antidepressants

The group of agents initially developed for the treatment of depression are often referred to as *antidepressants*. They have broad pharmacological effects, being antagonists at several receptors, including at least one wake-promoting system, which leads these medications to have sleep-promoting effects (Krystal 2010). These medications are used off-label for the treatment of insomnia, often at dosages lower than the antidepressant dosage. With a few exceptions, the risk-benefit profile of these antidepressant medications for the treatment of insomnia has not been evaluated in placebo-controlled trials. This is a significant limitation to their use in an evidence-based approach to insomnia therapy. However, it can be assumed that their nonspecific pharmacology leads them to have therapeutic effects on conditions other than insomnia--some of which are common comorbid conditions, such as depression, anxiety, and pain--but at the same time associates these medications with a relatively high side-effect burden (Krystal *et al.* 2013b).

Antidepressants used for the treatment of insomnia. The antidepressants most commonly used to treat insomnia include amitriptyline, doxepin, trimipramine, trazodone, and mirtazapine (Krystal 2010). Amitriptyline, doxepin (25-50 mg), and trimipramine promote sleep primarily through antagonism of norepinephrine, histamine, and acetylcholine receptors, whereas trazodone promotes sleep primarily through antagonism of norepinephrine, histamine, and serotonin type 2 ($5\text{-}HT_2$) receptors. Mirtazapine promotes sleep primarily through antagonism of histamine and $5\text{-}HT_2$ receptors.

Clinical therapeutic effects as indicated by available studies. Among the antidepressants used to treat insomnia, double-blind, placebo-controlled studies of insomnia treatment have been carried out only with trimipramine, doxepin (25-50 mg), and trazodone (Krystal 2010). Trimipramine has been studied at dosages from 50 mg to 200 mg and has been found to improve self-reported sleep quality and sleep efficiency (total sleep time/time in bed) but not sleep-onset latency (Hohagen *et al.* 1994; Riemann *et al.* 2002). Studies carried out with doxepin 25-50 mg indicated that, unlike with doxepin 3-6 mg, therapeutic effects on sleep onset, sleep maintenance, and sleep quality were seen (Hajak *et al.* 1996, 2001; Rodenbeck *et al.* 2003). Trazodone has been found to have therapeutic effects on sleep when used as adjunctive treatment to antidepressant medications in depressed patients with insomnia (Kaynak *et al.* 2004; Nierenberg *et al.* 1994). Trazodone (50 mg) also was evaluated in a placebo-controlled trial in patients with primary insomnia, and although improvement was reported in some sleep indices in the first week of treatment, trazodone's effects did not separate from placebo in the second week of this 2-week study (Walsh *et al.* 1998). A pilot trial of trazodone as a treatment for insomnia in abstinent alcoholic individuals suggested therapeutic effects on sleep-maintenance problems (Le Bon *et al.* 2003).

Effects on systems other than sleep-wake systems. All of the antidepressants with sleep-enhancing effects have effects on pharmacological systems other than those related to enhancing sleep. Some of these effects can be assets to therapy because they involve therapeutic effects on conditions that often co-occur with sleep disturbance (Krystal 2010; Krystal *et al.* 2013b). However, some non-sleep-related effects may lead to adverse effects. The specific adverse effects seen depend on both the mechanism of action and the dosage. The higher the dosage, the greater the effects on more pharmacological systems, including those mediating side effects. Agents with significant muscarinic receptor antagonism are associated with a risk of dry mouth, constipation, blurred vision, urinary retention, dizziness, memory impairment, and delirium (Krystal 2010; Krystal *et al.* 2013b). Antidepressants with significant adrenergic receptor antagonism are associated with a risk of orthostatic hypotension and dizziness (see appendix table at the end of this chapter). Weight gain, although incompletely understood, appears to be particularly likely with agents with histamine, 5-HT$_2$, and acetylcholine receptor antagonism.

Optimal target patient population. Antidepressants with sleep-enhancing effects are best suited for use by patients with sleep problems occurring in conjunction with a condition that these agents effectively treat. These conditions vary depending on the

medication but may include depression, anxiety, or pain (Krystal 2010) (see appendix table at the end of this chapter). Two main approaches are used for treating insomnia comorbid with another such condition. One is to administer single-agent therapy with one of these antidepressants at a dosage at which there are established antidepressant, anxiolytic, or pain effects. The other is to combine a sleep-targeted drug with a treatment aimed at improving the associated condition. No data indicate which approach is preferred. However, an advantage of the two-treatment approach is that it allows a wider range of treatments for the associated conditions, including nonsedating interventions. For example, in a depressed patient with insomnia disorder, one could combine bupropion as an antidepressant with a sleep-targeted intervention; bupropion alone lacks sleep-enhancing effects and thus could not reasonably be used as a single-agent therapy (Krystal *et al.* 2007b). Antidepressants also can be considered for use in treating treatment-resistant insomnia because of their broad pharmacological effects.

Antipsychotics

Antipsychotics share similarities to antidepressants in being medications with broad pharmacological effects that were developed for an indication other than insomnia disorder but are used off label in treating insomnia at lower-than-usual dosages. These agents were developed for the treatment of psychosis, although some have more recently received FDA indications for bipolar mania and depression as well. Like antidepressants, antipsychotics are antagonists at several receptors, at least one of which includes receptors of a wake-promoting system, which is the basis for their sleep-promoting effects (Krystal 2010; Krystal *et al.* 2008b). Very limited data are available on the risk-benefit profile of these medications for the treatment of insomnia. In fact, even fewer placebo-controlled trials have been carried out with antipsychotics than with antidepressants, which is a significant limitation to including antipsychotics in an evidence-based approach to insomnia therapy. However, it can be assumed that their nonspecific pharmacology leads them to have therapeutic effects on conditions other than insomnia--some of which are common comorbid conditions, such as schizophrenia, mania, delirium, depression, anxiety, and pain--but at the same time associates these medications with a relatively high side-effect burden (Krystal 2010; Krystal *et al.* 2008b, 2013b).

Antipsychotics used for the treatment of insomnia. The antipsychotics most commonly used to treat insomnia include olanzapine and quetiapine (Krystal 2010; Krystal *et al.* 2008b). Both of these agents promote sleep primarily through antagonism of histamine, norepinephrine, acetylcholine, 5-HT_2, and dopamine receptors (Krystal 2010; Krystal *et al.* 2008a).

Clinical therapeutic effects as indicated by available studies. No large-scale systematic studies of the use of any of these agents in the treatment of insomnia have been performed. Several small studies were carried out in healthy control subjects and patients with schizophrenia and mood disorders and included polysomnographic endpoints that provided a preliminary indication that olanzapine improves both sleep-onset and sleep-maintenance problems (Krystal 2010). An open-label trial of quetiapine 25-75 mg in primary insomnia patients provided preliminary evidence that this agent improves sleep-onset latency and total sleep time (Krystal 2010). A double-blind, placebo-controlled, randomized trial of quetiapine 25 mg was carried out in 13 insomnia patients but did not find any statistically significantly greater effects of drug compared with placebo (Tassniyom *et al.* 2010).

Effects on systems other than sleep-wake systems. All of the antipsychotics with sleep-enhancing effects have effects on pharmacological systems other than those related to enhancing sleep. Some of these effects can be assets to therapy because they involve therapeutic effects on conditions that often co-occur with sleep disturbance, including schizophrenia, mania, depression, anxiety, and pain (Krystal 2010; Krystal *et al.* 2008b). However, some non-sleep-related effects may lead to adverse effects. Like with antidepressants, the specific adverse effects seen with antipsychotics depend on both the mechanism of action and the dosage. The higher the dosage, the greater the effects on more pharmacological systems, including those mediating side effects (see appendix table at the end of this chapter). Those agents with significant dopamine receptor antagonism are associated with a risk of parkinsonian side effects, acute dystonic reactions, and tardive dyskinesia (Krystal *et al.* 2008b). Those with muscarinic cholinergic receptor antagonism are associated with a risk of dry mouth, constipation, blurred vision, urinary retention, dizziness, memory impairment, and delirium (Krystal 2010; Krystal *et al.* 2013b). Those with significant adrenergic receptor antagonism are associated with a risk of orthostatic hypotension and dizziness. Weight gain, although incompletely understood, appears to be particularly likely with agents with histamine, 5-HT_2, and acetylcholine receptor antagonism.

Optimal target patient population. Antipsychotics with sleep-enhancing effects are best suited for use by patients with sleep problems occurring in conjunction with a condition that the agents effectively treat. These conditions vary depending on the medication but may include schizophrenia, mania, delirium, depression, anxiety, or pain (Krystal 2010; Krystal *et al.* 2008a) (see appendix table). Antipsychotics also can be considered for use by treatment-resistant insomnia patients because of their broad pharmacological effects, but the cost of this relatively broad pharmacological effect is a relatively unfavorable side-effect profile that must be taken into account when deciding whether to administer these agents.

Conclusion

An increasing number of medications is becoming available to help patients with insomnia. For many years, investigators believed that the mechanism of action of insomnia medications was without clinical implications. Clinical effects were assumed to be determined primarily by dosage and drug pharmacokinetic properties. It is now clear that this is not the case. The mechanism of action matters. Clinical effects reflect not only dosage and pharmacokinetics but also the specific properties of the pharmacological system(s) being modulated by a given drug and the nature and state of other parallel pharmacological systems that continue to function during the period of action of that drug. As a result, factors such as time of day, the behavior of the patient, and the patient's psychosocial context (e.g., stress, novelty, excitement) can play a role in determining the clinical effects of medications used to treat insomnia. This has become apparent only through experience with the relatively more recently available agents, including selective antagonists of a single wake-promoting system. In comparison with older, more broadly acting agents, these medications promise an improved risk-benefit ratio for specific subgroups of patients who have the particular type of sleep problem targeted by the given selective wake-promoting system antagonist. Taking advantage of this potential requires knowledge of the specific clinical effects of each agent and the type of sleep difficulty that they best treat. It is also important to appreciate the instances when it is best to use a nonselective, more broadly acting agent. Knowledge of the properties of each agent and the best target patient subpopulation can then serve as a basis for optimally matching patients to therapies in clinical practice.

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APPENDIX

Properties of Agents Commonly Used to Treat Insomnia

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Properties of agents commonly used to treat insomnia

Agent	Enhancement of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target sleep aspect[a]	Common adverse effect
Benzodiazepines							
Triazolam	GABA	--	Insomnia	0.125-0.8	2-5.5	Onset and maintenance	Motor and cognitive impairmen abuse potential, sedation
Temazepam	GABA	--	Insomnia	7.5-30	8-20	Onset and maintenance	Motor and cognitive impairmen abuse potential, sedation
Flurazepam	GABA	--	Insomnia	15-30	40-250	Onset and maintenance	Motor and cognitive impairmen abuse potential, sedation
Lorazepam	GABA	--	Anxiety, status epilepticus	0.125-1	12-15	None	Motor and cognitive impairmen abuse potential, sedation
Clonazepam	GABA	--	Panic disorder, seizures	0.25-2	35-40	None	Motor and cognitive impairmen

Note. 5-HT = serotonin; Ach = acetylcholine; COPD = chronic obstructive pulmonary disease; DA = dopamine; HA = histamine; N/A = not applicable; N

[a]At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance, or end-of-night sleep difficulty.

Agent	Enhancement of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target sleep aspect[a]	Common adverse effect
							abuse potential, sedation
Alprazolam	GABA	--	Anxiety, panic disorder	1-3	12-14	None	Motor and cognitive impairmen abuse potential, sedation
Nonbenzodiazepines							
Zolpidem	GABA	--	Insomnia: sleep onset	5-10	2.0-5.5	Onset	Motor and cognitive impairmen abuse potential
Zolpidem extended release	GABA	--	Insomnia: sleep onset; sleep maintenance in first 6 hours of the night	6.25-12.5	2.0-5.5	Onset and maintenance	Motor and cognitive impairmen abuse potential, dizziness, somnolenc
Zolpidem sublingual	GABA	--	Insomnia: middle of the night	1.75-3.5	2.0-5.5	Middle-of-the-night insomnia	Motor and cognitive impairmen abuse potential
Zaleplon	GABA	--	Insomnia: middle of the night	10-20	0.9-1.1	Onset and middle-of-the-night insomnia	Motor and cognitive impairmen abuse potential
Eszopiclone	GABA	--	Insomnia: sleep onset and sleep maintenance	1-3	6-7	Onset and maintenance	Motor and cognitive impairmen abuse potential, sedation, metallic ta

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Note. 5-HT = serotonin; Ach = acetylcholine; COPD = chronic obstructive pulmonary disease; DA = dopamine; HA = histamine; N/A = not applicable; N

[a] At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance, or end-of-night sleep difficulty.

Agent	Enhancement of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target sleep aspect[a]	Common adverse effect
Selective melatonin receptor agonists							
Melatonin	Melatonin	--	N/A (available over the counter as herbal supplement)	0.3-10	0.6-1	Onset	Minimal
Ramelteon	Melatonin	--	Insomnia: sleep onset	8	0.8-2	Onset	Minimal
Selective histamine 1 receptor antagonist							
Doxepin	--	HA	Insomnia: sleep maintenance	3-6	10-50	Maintenance	Nausea, uppe respiratory infection, sedation

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Note. 5-HT = serotonin; Ach = acetylcholine; COPD = chronic obstructive pulmonary disease; DA = dopamine; HA = histamine; N/A = not applicable; N

[a] At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance, or end-of-night sleep difficulty.

Agent	Enhancement of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target sleep aspect[a]	Common adverse effect
Selective hypocretin/orexin receptor antagonists							
Suvorexant	--	Hypocretin/orexin	Insomnia: sleep onset and maintenance	10-20	9-13	Onset and maintenance	Cough, dry mouth, fatigue, abnormal dreams, headache, sedation
Lemborexant	--	Hypocretin/orexin	Insomnia: sleep onset and maintenance	5-10	17-19	Onset and maintenance	Abnormal dreams, headache, sedation
Daridorexant	--	Hypocretin/orexin	Insomnia: sleep onset and maintenance	25-50	8	Onset and maintenance	Fatigue, sedation, headache, nausea
Alpha-1 Adrenergic receptor antagonists							
Prazosin	--	NE	Hypertension	2-15	2-3	Maintenance in PTSD patients	Dizziness, nasal congestion dry mouth, sweating, orthostatic hypotensio
Nonspecific wake-promoting system antagonists							
Diphenhydramine	--	HA, Ach	Over-the-counter sleep and allergy medication	25-50	5-11	Maintenance	Sedation, dizziness, dry mouth, blurred vision, constipatio urinary retention
Nonspecific wake-promoting system antagonists *(continued)*							
Doxylamine	--	HA, Ach	Over-the-counter sleep and allergy medication	25-50	10-12	None	Sedation, dizziness, dry mouth, blurred vision, constipatio

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Note. 5-HT = serotonin; Ach = acetylcholine; COPD = chronic obstructive pulmonary disease; DA = dopamine; HA = histamine; N/A = not applicable; N

[a]At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance, or end-of-night sleep difficulty.

Agent	Enhancement of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target sleep aspect[a]	Common adverse effect
							urinary retention
Amitriptyline	--	NE, HA, Ach	Depression	10-100	10-100	None	Sedation, dizziness, weight gai orthostatic hypotensio dry mouth, blurred vision, constipatio urinary retention
Doxepin	--	NE, HA, Ach	Depression	25-75	10-50	Onset and maintenance	Sedation, dizziness, weight gai orthostatic hypotensio dry mouth, blurred vision, constipatio urinary retention
Trimipramine	--	NE, HA, Ach	Depression	25-100	15-40	Maintenance	Sedation, dizziness, weight gai orthostatic hypotensio dry mouth, blurred vision, constipatio urinary retention

Note. 5-HT = serotonin; Ach = acetylcholine; COPD = chronic obstructive pulmonary disease; DA = dopamine; HA = histamine; N/A = not applicable; N

[a] At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance, or end-of-night sleep difficulty.

Agent	Enhancement of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target sleep aspect[a]	Common adverse effect
Nonspecific wake-promoting system antagonists *(continued)*							
Trazodone	--	5-HT_2, NE, HA	Depression	25-150	7-15	None	Sedation, dizziness, headache, dry mouth, blurred vision, orthostatic hypotensio priapism
Mirtazapine	--	5-HT_2, HA	Depression	7.5-30	20-40	None	Sedation, dry mouth, increased appetite, weight gai constipatio
Olanzapine	--	HA, NE, Ach, 5-HT_2, DA	Psychosis	2.5-20	20-54	None	Sedation, agitation, dizziness, constipatio orthostatic hypotensio akathisia, weight gai increased risk of cerebrovas lar events i dementia
Quetiapine	--	HA, NE, Ach, 5-HT_2, DA	Psychosis	25-200	7	None	Sedation, orthostatic hypotensio dry mouth, tachycardi weight gai

Note. 5-HT = serotonin; Ach = acetylcholine; COPD = chronic obstructive pulmonary disease; DA = dopamine; HA = histamine; N/A = not applicable; N

[a] At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance, or end-of-night sleep difficulty.

CHAPTER 59

Treatment of Chronic Pain

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Pain is the most common symptom reported both by the general population and in the general medical setting (Kroenke 2003). Chronic pain is associated with decreased quality of life, opioid dependence, and poor mental health. According to the National Center for Health Statistics (Zelaya *et al.* 2020), in 2019 the prevalence of chronic pain in U.S. adults was 20.4%, and high-impact chronic pain, defined as pain that frequently limits life or work activities, was found in 7.4% of adults. The prevalence of pain increased with age and was highest (30.8%) in adults ages 65 years and older. Women, people from lower socioeconomic backgrounds, military veterans, and rural residents have been noted to have higher rates of chronic pain (Dahlhamer *et al.* 2018). In a report published in 2011, the Institute of Medicine estimated that chronic pain affected one in three Americans and resulted in medical costs and lost productivity amounting to $560-$635 billion annually.

Psychiatric Comorbidity

Pain is more prevalent in patients with psychiatric comorbidity (particularly mood disorders) than in those without, and it is a strong predictor of both the onset and persistence of depression (Ohayon and Schatzberg 2003).

Depression is likewise a powerful predictor of pain, particularly persistent pain (Bair *et al.* 2003; Gureje *et al.* 1998). Concurrent pain and depression have a much greater impact than either disorder alone on multiple domains of functional status as well as health care utilization. Comorbid depression worsens disability and decreases active coping in patients with pain (Arnow *et al.* 2006; Demyttenaere *et al.* 2008). Comorbidity decreases the likelihood of a favorable response of either condition to treatment and diminishes patient satisfaction with treatment (Bair *et al.* 2004; DeVeaugh-Geiss *et al.* 2010; Karp *et al.* 2005; Kroenke *et al.* 2008; Mavandadi *et al.* 2007; Thielke *et al.* 2007). Reliable methods

for assessing the presence and severity of pain in patients with depression, particularly those not responding to initial treatment, and strategies for effectively and efficiently integrating evidence-based depression care into the management of patients with chronic pain are sorely needed.

Although not as extensively studied, the comorbidity of pain with anxiety appears to be nearly as strong as its comorbidity with depression (Bair *et al.* 2008; Kroenke 2003; Kroenke and Price 1993; McWilliams *et al.* 2003). A global study conducted by the World Health Organization in 17 countries and involving more than 85,000 community-dwelling adults showed that pain is associated with mood and anxiety disorders, but not with alcohol use disorders (Gureje *et al.* 2008). In this study, the prevalence of specific mood and anxiety disorders was lowest among persons with no pain, intermediate among those with one pain site, and highest among those with multiple pain sites. Relative to persons not reporting pain, the age-sex adjusted odds ratios were 1.8 (95% CI = 1.7-2.0) for mood disorders and 1.9 (95% CI = 1.8-2.1) for anxiety disorders among persons with single-site pain, and 3.7 (95% CI = 3.3-4.1) for mood disorders and 3.6 (95% CI = 3.3-4.0) for anxiety disorders among those with multisite pain.

Definition and Classification of Pain

The International Association for the Study of Pain (IASP; 2012) defined pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Although there are more complex approaches to classifying pain, a common approach broadly classifies pain as either nociceptive or neuropathic.

Nociceptive pain includes most cases of acute pain in which a strong, noxious stimulus impacts the skin or deep tissue. Acute pain resolves after the noxious stimulus has been removed, but inflammatory and other mechanisms may lead to the persistence of nociceptive pain for weeks, months, or years (i.e., chronic pain). Many pain conditions, including arthritis and other musculoskeletal disorders, migraine and tension headache, and chronic widespread pain conditions such as fibromyalgia, would be classified under the broad rubric of nociceptive pain.

Nociceptive pain can be further divided into somatic pain (triggered in the skin, muscles, joints, or fascia) and visceral pain (in the heart, lungs, gastrointestinal or genitourinary systems, or other deeper organs). Somatosensory fibers are precisely located in the spinal cord and brain, whereas afferent viscerosensory fibers overlap each other and converge at several levels within the nervous system. Visceral pain is diffuse and poorly localized, reflecting differences in innervation between somatic and visceral tissue.

Neuropathic pain arises from injury to the peripheral nervous system or CNS. Examples include postherpetic neuralgia, painful diabetic neuropathy, phantom limb pain, and sciatica. Neuropathic pain is often characterized as burning, paroxysmal, stabbing, buzzing, or electric shock-like. Some conditions, such as low back pain, may include both nociceptive components (arising from the muscles or contiguous tissues) and neuropathic components (radicular pain or sciatica).

Persons with chronic pain often have spontaneous ongoing pain. Allodynia is a condition in which pain due to a normally painless stimulus, like light touch, causes pain. Hyperalgesia

is a similar pain condition in which a stimulus that typically would produce mild pain instead causes much greater pain than would normally be expected. These phenomena may be related to central sensitization, which has been proposed as a common mechanism underlying unexplained pain syndromes such as fibromyalgia.

In this chapter we concentrate on the management of chronic pain due to nociceptive pain of the somatic variety and neuropathic pain conditions. Together these conditions account for the majority of chronic pain conditions seen in clinical practice. Of note, visceral pain is more commonly a harbinger of a serious underlying disorder, with specific treatments targeting the disease itself rather than mere analgesia.

Treatment of Pain

Overview

The focus of this chapter is twofold. First, we discuss major classes of medications as they relate to pain management. Because a number of drugs are effective across multiple types of pain disorders, it is useful to consider them in a cross-cutting as well as a disease-specific fashion. Second, nonpharmacological treatments are also reviewed. In the "Selected Pain Disorders" section we address several specific categories of disorders chosen because they account for the most common types of chronic pain, are conditions for which pain management is the principal focus, and have been studied in numerous clinical trials. Prevalence, pain management as a priority over disease modification, and evidence-based therapy are the three selection criteria for the discussion of specific disorders.

The prototypical diseases discussed are musculoskeletal disorders (principally fibromyalgia, low back pain, and osteoarthritis), headaches, and neuropathic pain. Acute pain (e.g., injuries, postoperative pain), cancer pain, and visceral pain are not addressed. Although pharmacotherapy receives the greatest attention in this chapter, we briefly review some nonpharmacological treatments used in the management of chronic pain.

Pharmacotherapy

Nonopioid Analgesics

The antiinflammatory properties of the extract of willow bark have been known for centuries. Salicylic acid was discovered as the extract's active ingredient in the nineteenth century and was subsequently acetylated to improve its gastrointestinal tolerability. Acetylsalicylic acid became the prototypical analgesic known as aspirin. Aspirin and other related compounds constitute a class of drugs known as nonsteroidal antiinflammatory drugs (NSAIDs). All NSAIDs have three desirable pharmacological effects: antiinflammatory, analgesic, and antipyretic effects. NSAIDs and acetaminophen are among the most commonly prescribed medications for pain.

Acetaminophen has analgesic and antipyretic effects similar to those of NSAIDs but notably lacks a specific antiinflammatory effect. Despite the widespread use of acetaminophen, its analgesic mechanism is poorly understood. Acetaminophen is a slightly weaker analgesic than NSAIDs (Towheed *et al.* 2006) but is a reasonable first-line option because of its more favorable safety profile and low cost. Acetaminophen is associated with asymptomatic elevations of aminotransferase levels at dosages of 4 g/day even in healthy adults, although the clinical significance of these findings is uncertain (Watkins *et al.* 2006). Thus, known liver disease is a reason either to use analgesics other than acetaminophen or to lower the maximum daily dose of acetaminophen to 2,000 mg or less.

NSAIDs block the enzymatic activity of cyclooxygenase (COX), which uses arachidonic acid to generate prostanoids. Prostanoids influence immune, cardiovascular, gastrointestinal, renovascular, pulmonary, CNS, and reproductive function. Although gastrointestinal adverse effects have traditionally been considered the most common and worrisome complication of use of nonsteroidal antiinflammatory drugs, cardiovascular risk has gained increasing attention (Antman *et al.* 2007).

There are two major COX isoenzymes: COX-1 is expressed constantly in most tissues, whereas COX-2 is induced by inflammation. NSAIDs vary in their chemical structure and relative ability to block the COX-1 versus COX-2 isoenzymes. Several prostaglandins are both hyperalgesic and gastroprotective. Thus, nonselective COX inhibition with NSAIDs like aspirin, ibuprofen, indomethacin, and naproxen, which inhibit both COX-1 and COX-2 enzymes, provides effective pain relief for inflammatory conditions but carries a risk for erosive gastritis and gastrointestinal bleeding. Selective COX-2 inhibitors (valdecoxib, rofecoxib, celecoxib) have less gastrointestinal toxicity because of the relative paucity of COX-2 expression in the gastrointestinal tract compared with inflammatory tissue. However, data from meta-analyses and registries have shown an increased risk of cardiovascular events and mortality from use of COX-2 inhibitors, particularly in patients with known cardiovascular disease who receive prolonged treatment. Rofecoxib (Vioxx) was withdrawn from the market in 2004, and all COX-2 inhibitors should be used cautiously, if at all, by patients with cardiovascular disease or risk factors for cardiovascular disease. All NSAIDs, including nonselective COX inhibitors and COX-2 agents, appear to be equally effective in the treatment of pain disorders (Chou *et al.* 2006). The NSAID that appears to be the safest in terms of cardiovascular risk is naproxen.

In July 2015, the FDA decided to strengthen its existing label warning that NSAIDs increase the chance of a heart attack or stroke. Although there is some risk even with short-term use or in patients without a history of cardiovascular disease or risk factors, both a longer duration of use and the presence of cardiovascular disease or risk factors substantially increase cardiovascular risk in patients receiving NSAIDs. However, the actual increased risk in a specific patient is still low. Given the prevalence of and disability associated with chronic pain and the limitations of other treatment options, NSAIDs are likely to remain a staple of pain management. Concerns about long-term use are focused on special populations, including those at greater risk for cardiovascular (e.g., known cardiovascular disease or more than two cardiovascular risk factors), gastrointestinal, or renal complications (Marks *et al.* 2012).

Opioid Analgesics

The analgesic effects of opium have been known for more than 5,000 years. However, their inherent abuse risk soon became evident. Ever since, society has attempted to find a balance between licit and illicit use, therapeutic and adverse effects, and medical needs and legal issues. Despite all the legal, administrative, and social interference associated with opioid use, no other class of drugs has remained in use for as long as opioids (Schug 2005).

Currently there are five known types of opioid receptors: mu (m), kappa (k), delta (d), nociceptin, and zeta (z). These receptors are responsible for the various physiological responses to opioid compounds. m Opioid receptors are related to analgesia, physiological dependence, euphoria, respiratory depression, miosis, constipation, and vasodilation. k Opioid receptor agonism causes analgesia, diuresis, and dysphoria. d Opioid receptors are related to analgesia and constipation. Nociceptin opioid receptors produce analgesia or hyperalgesia, depending on the concentration of the agonist present. z Opioid receptors are thought to be involved in cellular developmental processes unrelated to analgesia (Dhaliwal and Gupta 2023). Individuals vary in their sensitivity to the agonism of opioids at each receptor subtype, and also vary in cytochrome P450 (CYP) metabolism, receptor alleles, membrane transporters, and other factors. This heterogeneity gives rise to the variable clinical responses seen in terms of both analgesic benefit and side-effect burden (Smith 2008; Vieira *et al.* 2019).

Opioid treatment for chronic noncancer pain is typically reserved as a second-or third-line treatment because of ambiguity over the benefits of long-term opioid exposure and significant risks related to substance use disorders (SUDs), long-term effects (e.g., immunological, reproductive), opioid-induced hyperalgesia, and the increasingly complex regulatory environment.

The Controlled Substances Act of 1970 divided substances to be regulated into five schedules, as determined by the U.S. Drug Enforcement Administration. These schedules govern the legal distribution and use of most substances with a significant abuse liability. Schedule I drugs have the highest abuse potential. They are available for research only and have no approved medical uses. Schedule II-IV substances have decreasing abuse liabilities (II is the highest) and approved medical uses. Schedule II compounds have more stringent recordkeeping and storage requirements than Schedule III and Schedule IV substances. Schedule V substances have a recognized abuse liability but are generally not as highly regulated. Most opioids prescribed for pain are Schedule II substances, and each dispensation requires a new prescription. Notable exceptions are combination analgesics (e.g., those containing acetaminophen) that contain less than 90 mg of codeine per unit dose and buprenorphine, which are Schedule III substances. Tramadol, a centrally acting opioid analgesic with weak serotonin and norepinephrine reuptake inhibition, is a Schedule IV substance.

Opioids were initially reserved for short-term treatment of acute pain from conditions like surgery or trauma and palliation for cancer and other terminal diseases. In the 1990s advocacy for more aggressive treatment of chronic pain led to a sharp increase in the prescription of opioids (Nuckols and Chou 2014). An unintended consequence of this expansion of opioid availability was an increase in opioid use disorders. A total of 70,630 drug overdose deaths occurred in the United States in 2019, with around half of them involving synthetic opioids. The age-adjusted rate of synthetic opioid deaths rose from 1.0 per 100,000 to 11.4 per 100,000 between 2013 and 2019, an astounding 1,040% increase (Mattson *et al.* 2021). State and federal regulations are now being enacted to more closely regulate opioid prescription and dispensation to minimize the ongoing public health crisis.

Efficacy and adverse effects of opioids. Opioids continue to play a central role in the treatment of chronic pain, but the evidence supporting their use is not unequivocally supportive and serious risks are known. In two large systematic reviews (Busse *et al.* 2018; Chou *et al.* 2015) there were no studies that compared opioid-based treatment of chronic pain with nonopioid pain treatment strategies over 1 year or longer. There was clear evidence accumulating for the risk of serious harms with long-term opioid exposure, including overdose, abuse and misuse, fractures, myocardial infarction, motor vehicle accidents, and sexual dysfunction. Notably, no study in the analyses evaluated risks related to cognitive function; fall risk; infections; psychological changes; or the effectiveness of strategies to mitigate the risk of misuse, overdose, or the development of SUD (Chou *et al.* 2015).

When compared with placebo, opioids demonstrated small improvements in pain, physical function, and sleep quality that diminished over time and were notably reduced in studies longer than 3 months. A small but nonsignificant benefit in social function was seen, whereas no improvement in emotional function or role function was found compared with placebo (Busse *et al.* 2018). Opioids had side effects in excess of those seen with placebo related to vomiting, drowsiness, constipation, dizziness, nausea, dry mouth, and itching.

Opioids had benefits similar to NSAIDs, tricyclic antidepressants (TCAs), or nabilone (a cannabinoid) without evidence of superiority for pain relief or improvement in physical function. Opioids showed a small degree of superior pain relief compared with anticonvulsants. All of this evidence was found in studies of only 1-6 months' duration. Notably, there was not an association between opioid dosing and any of the outcomes. There likewise did not appear to be differential benefit for different pain conditions (e.g., neuropathic vs. nociceptive pain) from opioid treatment (Busse *et al.* 2018).

Evidence of the effect of opioid therapy for chronic pain on cognition is of limited quality and quantity but suggests that long-term exposure may negatively affect attention, language, orientation, psychomotor function, and several domains of memory (verbal/short term, episodic). It is notable that some studies show elements of improved cognition with opioid therapy, and it is speculated that this could be a benefit of improved pain control (Pask *et al.* 2020).

Endocrinological derangements from long-term opioid exposure are not uncommon. Proposed mechanisms for these changes include inhibition of gonadotropin-releasing hormone and stimulation of prolactin secretion. Hypogonadism, which is estimated to occur in more than 60% of male patients on long-term opioids, can manifest as sexual dysfunction and low libido. Male patients may report erectile problems, anorgasmia, or gynecomastia. Female patients' symptoms will more likely relate to menstrual irregularity. Hypercortisolism, which is estimated to occur in 15%-24% of individuals taking long-term opioids, may manifest as fatigue, malaise, anorexia, orthostasis, or abdominal discomfort. It is prudent to monitor all patients on long-term opioids for endocrine derangements related to testosterone, cortisol, and prolactin secretion (de Vries *et al.* 2020).

Tolerance and substance use disorders. The risks of prescription opioid addiction, abuse, and diversion among chronic pain patients are not well understood. In part this is because of inconsistent use of terminology and nuances among tolerance, physiological dependence, abuse, addiction, and SUD. Tolerance is the development of decreased responsiveness to a substance that may require dose escalation for continued equivalent benefit. Physiological dependence, which may occur in tandem

with tolerance, is the development of physiological need for continued administration of a substance to avoid withdrawal symptoms.

The stigmatizing terms *abuse* and *addiction* are now avoided in favor of *substance use disorder* defined in terms of mild, moderate, or severe degree. DSM-5 defines SUDs on the basis of 11 different criteria in the four major domains of impaired control over substance use, social problems as a consequence of substance use, risky use, and physiological tolerance or withdrawal (American Psychiatric Association 2013).

The evidence around SUDs and opioid treatment for chronic noncancer pain is of limited quality and quantity. Patients with SUD are typically excluded from studies of chronic pain intervention, which creates a vacuum of good data on this increasingly large population. Opioid management in patients with active or historical SUD is more complex, and close monitoring of analgesia, changes in activities of daily living, adverse reactions, and behaviors suggesting aberrant opioid use is recommended. The existing data suggest that the prevalence of SUDs in persons with chronic noncancer pain is relatively high, with estimates of the prevalence of active SUD ranging from 3% to 48%. Patients with a history of SUD are at increased risk for opioid misuse, but there are not sufficient data to reliably quantify the risk. Patients with SUD who adhere to treatment appear to receive pain relief benefits similar to those received by patients without SUD (Morasco *et al.* 2011). Another systematic review found that 11.5% of patients with chronic noncancer pain who were prescribed opioids developed aberrant medication use behaviors. Studies that specifically excluded patients with a history of SUD saw only 0.6% of participants develop aberrant medication behaviors (Fishbain *et al.* 2008). Notably, patients with other psychiatric comorbidity, particularly anxiety and depressive disorders, are at higher risk for the development of problematic opioid use when treated for chronic pain (van Rijswijk *et al.* 2019). All patients being treated for chronic pain with or without opioids should be screened periodically for psychiatric comorbidities.

General principles of opioid use. Opioids should be used judiciously and sparingly in the management of chronic pain, given the limitations of supporting evidence and the known risks we have outlined. Patients should understand that the goal of treatment is not the complete elimination of pain but a 25%-50% reduction in its intensity and improvement in mood and function. Opioid therapy should be initiated with less potent agents with escalation to higher doses or more potent agents as needed.

The use of heroically high doses of opioids is rarely helpful. The highest daily dose of opioids used in existing trials is 180 mg of morphine or its equivalent, and in typical clinical contexts, opioid reduction or rotation should be considered at this point or earlier. The initial dosage of a new opioid should be equivalent to 50% or less of the dosage of the original opioid because of incomplete cross-tolerance. Approximate equianalgesic doses of oral and transdermal opioids are summarized in Table 59-1. It should be noted that these values are based on limited data and that opioid effects can vary significantly among individuals in terms of analgesia and side effects.

TABLE 59-1. Oral and transdermal analgesic equivalence of commonly used opioids

Drug	Dose (mg)	Duration (hours)[a]

[a] The duration of analgesia is dose dependent; the higher the dose, usually the longer the duration.

[b] These high doses of codeine and meperidine are not recommended clinically.

[c] Equianalgesic data are more variable for hydrocodone than for most other opioids.

[d] For opioid-tolerant patients converted to methadone, starting doses should be 10%-25% of the equianalgesic dose. Also, the half-life of methadone can vary widely, from 12 to 190 hours.

[e] 1 mg/hour transdermally is approximately equal to morphine 2 mg/24 hours orally.

Drug	Dose (mg)	Duration (hours)[a]
Morphine	30	2-4
Codeine	200[b]	3-4
Hydrocodone	30-40[c]	4-6
Oxycodone	20	4-4
Hydromorphone	7.5	4-4
Meperidine	300[b]	4-4
Methadone	20[d]	4-8
Fentanyl (transdermal)	12.5 mg/hour[e]	48-72

[a] The duration of analgesia is dose dependent; the higher the dose, usually the longer the duration.

[b] These high doses of codeine and meperidine are not recommended clinically.

[c] Equianalgesic data are more variable for hydrocodone than for most other opioids.

[d] For opioid-tolerant patients converted to methadone, starting doses should be 10%-25% of the equianalgesic dose. Also, the half-life of methadone can vary widely, from 12 to 190 hours.

[e] 1 mg/hour transdermally is approximately equal to morphine 2 mg/24 hours orally.

Opioid rotation is the practice of changing a drug or route of administration to achieve better outcomes in terms of either analgesia, side effects, or both. Potential indications for opioid rotation may include intolerable side effects; inadequate analgesia despite dose escalation; problematic drug interactions; the need for a new route of administration; or a change in clinical status that may affect pharmacokinetics, such as renal or hepatic impairment (Fine and Portenoy 2009).

The equianalgesic table was developed in 1966 and has been modified very little since that time (Houde *et al.* 1966). Advancements in our understanding of the complexity of opioid response, including incomplete cross-tolerance and variability among individuals, have given rise to a recommended two-step process to safely cross over from one opioid to another. This method reduces risks of accidental overdose while attempting to maintain adequate analgesia. First, calculate the equianalgesic dose of the new opioid using the equianalgesic table and initiate the new opioid at 25%-50% of the calculated equianalgesic dose. Second, rapidly reassess pain and adjust the dose up or down by 15%-30% depending on the clinical response to the initial dose. Two notable exceptions are methadone, which requires an initial dose reduction of 75%-90%, and transdermal fentanyl, which should be dosed according to the tables found in the package (Fine and Portenoy 2009).

When trials of several opioids are ineffective in treating chronic pain, it is appropriate to consider tapering and discontinuation of opioid therapy. Tapering schedules will vary among individuals, and care should be taken to avoid precipitating withdrawal or pain crisis with overly aggressive reduction timelines. For patients on high doses, outpatient discontinuation may be a process that can take months. A gentle schedule of 5%-20% dose reduction every 4 weeks may be optimal for patients with a longer duration of opioid treatment. Some patients with shorter exposure or lower doses may tolerate a 5%-20% reduction per week. In cases of SUD, referral to an SUD specialist may be optimal so that a more comprehensive, psychosocially informed plan can be made to manage the patient's pain and SUD together (Rosenberg *et al.* 2018). A review of 13 guidelines addressing opioid prescribing in adults with chronic pain found that most guidelines recommend that clinicians 1) avoid daily doses greater than 90-200 mg of morphine equivalents (ideally less than 100 mg); 2) have additional knowledge to prescribe methadone (as well as buprenorphine); 3) recognize

the risks of fentanyl patches, titrate cautiously, and reduce doses by at least 25%-50% when switching opioids; and 4) use opioid risk assessment tools, written treatment agreements, and urine drug testing to mitigate risks (Nuckols and Chou 2014). However, most recommendations are supported by observational data or expert consensus rather than findings from clinical trials. Principles for the use of opioids in the treatment of chronic pain are summarized in Table 59-2.

TABLE 59-2. Opioid management strategy for the treatment of chronic pain

1. Maximize nonopioid analgesic strategies first.
2. Inform patient of risks, including substance use disorder, before initiating opioid therapy.
3. Although the evidence is not strong, four strategies are variably encouraged by some expert pain groups or are mandated by prescribing regulations in some states:
    a. Opioid risk tools: Stratify risk with screening measures such as the Opioid Risk Tool and the Screener and Opioid Assessment for Patients with Pain.
    b. Opioid agreements (contracts): Consider the use of opioid agreements (contracts) for patients initiating or increasing opioids. Key points to stipulate include the frequency of obtaining medications, timely refills but no early replacement of lost or stolen prescriptions, safe storage, no sharing, single-source prescribing, monitoring through urine screens, and adherence to monitoring visits. The benefit of these agreements and their medicolegal validity is not well established.
    c. Urine drug screening: Conduct initial and periodic urine drug screening for opioids as well as illicit drugs.
    d. Prescription drug monitoring program: Use the state prescription drug monitoring program to monitor all sources of controlled substances.
4. Immediate-release opioids are recommended for initial therapy and breakthrough pain, although sustained-released opioids may have an important role in long-term therapy.
5. A short-acting opioid dose is typically 10%-20% of the total daily dose (e.g., if 24-hour scheduled morphine totals 50 mg, give 5-10 mg short-acting morphine for breakthrough pain).

Source. Adapted from Chou *et al.* 2014; Dowell *et al.* 2016; Nuckols and Chou 2014; Reuben *et al.* 2015.

6. Schedule follow-up visits at 2-to 3-month intervals, performing periodic urine testing to confirm adherence.
7. Monitor pain severity and pain-related functional impairment at follow-up visits to guide analgesic dose adjustments.
8. Avoid escalating the opioid dose without first assessing pain severity and interference.
9. View opioid initiation as an empirical trial. Consider discontinuing opioids if they are not beneficial.
10. Consider opioid rotation if inadequate response to one opioid occurs. Reduce the morphine-equivalent dose (MED) of the new opioid by 3%-50% to accommodate for unknown cross-tolerance and then titrate to goal.
11. If the patient is a high-risk candidate for opioids, consider referral to a pain specialist.
12. Minimize the use of sedative-hypnotics, benzodiazepines, and other controlled substances.
13. Consider referral to a pain specialty program if the MED exceeds 80-120 mg/day.

Source. Adapted from Chou *et al.* 2014; Dowell *et al.* 2016; Nuckols and Chou 2014; Reuben *et al.* 2015.

Long-acting opioids. A systematic review (Carson *et al.* 2011) compared the effectiveness and harms of long-acting opioids and also compared long-acting opioids with short-acting opioids in adults with chronic noncancer pain. The evidence was insufficient

to determine whether there are differences among long-acting opioids in effectiveness or harms, and no difference was found in pain relief or functional outcomes among various long-acting opioids. Evidence was insufficient to determine whether long-acting opioids as a class are more effective or are associated with fewer harms than short-acting opioids.

Methadone.

Methadone is a long-acting full agonist analgesic that is effective for pain control and also has been widely used as a maintenance drug in the treatment of opioid use disorder. The stigma from its reputation as a drug for addicts has been a factor limiting its use as an analgesic in clinical practice. It is commonly used in the treatment of intractable pain in end-of-life care and other palliative care settings. Concerns regarding the use of methadone to treat pain relate to its long and unpredictable half-life, which carries the risk of a delayed overdose in the days immediately following dose escalation. Large variations in equianalgesic doses of methadone relative to other opioids have been seen among individuals. This confounds the use of simple equianalgesic tables to calculate the required dose of methadone during rotation from other opioids. Despite the long half-life of methadone and its metabolites, dosing is required three to four times daily for optimal analgesia.

Although methadone has increasingly been used for the treatment of chronic noncancer pain, published data are rather modest. The current evidence base is inadequate and does not support methadone as a first-line treatment for chronic pain (Sandoval *et al.* 2005).

Regarding safety, a review of 168 studies found insufficient evidence to answer most safety questions, including risk factors associated with methadone overdose deaths and adverse events; the comparative mortality of methadone versus other opioids; the harms associated with methadone use during pregnancy; and the effects of risk mitigation strategies such as electrocardiogram monitoring, strategies for managing patients with prolonged QTc intervals on screening, urine drug testing, alternative dosing regimens for initiation and titration of therapy, and timing of follow-up (Weimer and Chou 2014).

Buprenorphine. Buprenorphine was introduced into the United States in 1985 as an opioid analgesic and like other opioids was found to have the potential to be abused intravenously. The opioid receptor antagonist naloxone was added to reduce the abuse potential, and the combination of buprenorphine and naloxone (Suboxone) was approved by the FDA in 2002 as a Schedule III drug for office-based SUD treatment. Compared with other opioids, buprenorphine has a somewhat lower potential for SUD because of partial agonism at opioid receptors rather than full agonism. The partial agonism produces less respiratory depression and other side effects than full agonism. The low dose of naloxone contained in the combination of buprenorphine and naloxone can reverse opioid effects if an attempt is made to use the combination preparation intravenously. When taken orally, as intended, the naloxone is not significantly bioavailable and does not interfere with the opioid activity of the buprenorphine.

Buprenorphine/naloxone is a sublingual combination tablet composed of buprenorphine and naloxone in a fixed 4:1 ratio. Although FDA approved only for SUD treatment, the combination can be effectively used off-label as a treatment for pain. This is particularly the case for patients currently or previously on opioids who have developed tolerance or, alternatively, SUD problems. For many years, all buprenorphine preparations required special credentialing, but in early 2021, federal regulations were updated to allow all prescribers to treat up to 30 patients without undergoing additional training and certification.

Buprenorphine preparations are typically prescribed once daily for medication-assisted treatment of opioid use disorder and suppression of opioid craving. Analgesic uses require dosing three to four times daily to achieve optimal pain control. Buprenorphine can be particularly useful for the management of opioid analgesia in patients with SUDs because of its utility in reducing opioid craving, availability in diversion-resistant preparations (i.e., the combination of buprenorphine and naloxone), and safety in overdose.

The initiation of buprenorphine in patients already taking opioids must be done with care as the partial agonist buprenorphine will displace other opioids from opioid receptors and induce acute withdrawal symptoms. To avoid the precipitation of acute withdrawal and possibly pain crisis, patients should stop their current opioids and take an initial dose of buprenorphine only after beginning to show mild signs of opioid withdrawal.

Antidepressants

Tricyclic antidepressants.

TCAs have been used for many years in the treatment of a wide variety of pain conditions. Lower dosages of TCAs have been used in clinical trials of pain management (e.g., 25-100 mg/day of amitriptyline or equivalent) compared with the dosages used for treating depression. The mechanism of action of TCAs is similar to that of the newer class of serotonin-norepinephrine reuptake inhibitors (SNRIs), and their benefit in pain conditions is thought to occur through similar pathways.

Advantages of TCAs include good evidence from multiple clinical trials, decades of clinical experience with TCAs in pain management, and the low cost of these generic agents. Disadvantages of TCAs include side effects like cardiovascular concerns (hypertension, postural hypotension, arrhythmias), an increased risk of falls in elderly patients, and potential lethality in overdose.

Selective serotonin reuptake inhibitors. Although selective serotonin reuptake inhibitors (SSRIs) may be useful in the co-management of anxiety and depression in the context of pain, their efficacy and adjuvant analgesics have not been clearly established. Existing data are heterogeneous and of low quality, which precludes clear recommendation of their use in the treatment of chronic pain (Patetsos and Horjales-Araujo 2016).

Serotonin-norepinephrine reuptake inhibitors. ***Duloxetine.*** A review of 30 trials involving individuals with diabetic neuropathy (12 trials), fibromyalgia (9 trials), low back pain (6 trials), and osteoarthritis (3 trials) found that the SNRI antidepressant duloxetine at a dosage of 60 mg once daily was effective in reducing pain in all four conditions (Pergolizzi *et al.* 2013). Duloxetine showed a rapid onset of action, with separation from placebo beginning at week 1. In a number of trials, both patients with depression and those without depression were enrolled, although path analysis estimated that more than two-thirds of the analgesic effect in duloxetine-treated patients was attributable to a direct analgesic effect, with less than one-third possibly explained by an antidepressant effect (Brannan *et al.* 2005; Brecht *et al.* 2007; Marangell *et al.* 2011; Perahia *et al.* 2006).

Milnacipran. Approved some years ago in Europe for the treatment of depression, milnacipran is comparable to SSRIs as an antidepressant (Papakostas and Fava 2007). Although milnacipran is FDA approved only for the treatment of fibromyalgia, levomilnacipran (an enantiomer of milnacipran branded Fetzima) is FDA approved for the treatment of depression. Substantial data confirm the effectiveness of milnacipran 100 mg/day or 200 mg/day for fibromyalgia-related pain, although there are not adequate data to demonstrate its efficacy for neuropathic pain (Derry *et al.* 2012). A meta-analysis of 5 milnacipran trials (4,129 patients), 4 duloxetine trials (1,411 patients), and 10 amitriptyline trials (612 patients) showed all three drugs to be superior to placebo, with small differential effects of the drugs on several fibromyalgia symptoms but overall similar acceptability and effectiveness (Hauser *et al.* 2011). However, the methodological quality of the amitriptyline trials was poor compared with that of the trials of the other two drugs.

Venlafaxine. There is only modest evidence for the efficacy of venlafaxine in treating fibromyalgia--four open-label cohort studies and one randomized trial (VanderWeide *et al.* 2015). Evidence of limited quality exists supporting its efficacy in the broad category of neuropathic pain (Aiyer *et al.* 2016). Although used clinically in treating many pain conditions, venlafaxine is not FDA approved for any pain disorder, and high-quality evidence supporting its broad use remains to be found.

Other antidepressants. Mirtazapine was studied in a 6-week open-label trial of 594 patients with a primary diagnosis of at least one chronic pain syndrome ([?] 3 months) and a clinical diagnosis of depression (Freynhagen *et al.* 2006). The mean daily dose was 35 +- 10 mg at study endpoint, and a statistically significant reduction in pain ($P < 0.0001$) was found. Pain improvement was not related to age or type of pain syndrome.

Anticonvulsants

Anticonvulsant drugs have been used in the management of pain since the 1960s. The clinical impression is that they are useful for treating chronic neuropathic pain, especially when the pain is lancinating or burning. Three of the most extensively studied anticonvulsants are gabapentin, pregabalin, and carbamazepine. Gabapentin and pregabalin have the strongest evidence for the treatment of pain. These two gabapentinoids act as neuromodulators by selectively binding to the a_2d-subunit-subunit protein of calcium channels in various regions of the brain and the superficial dorsal horn of the spinal cord. This results in inhibition of the release of excitatory neurotransmitters that are important in the production of pain. Gabapentin and pregabalin are analogs of GABA, but they have no activity at GABA receptors and do not alter GABA uptake or degradation.

Gabapentin. Gabapentin has been widely used to treat neuropathic pain of all types. A systematic review updated in 2015 concluded that gabapentin in dosages of 1,800 mg/day to 3,600 mg/day, typically divided into three daily doses, can provide good relief from pain for people with postherpetic neuralgia (number needed to treat [NNT] = 6.7) and diabetic peripheral neuropathy (NNT = 6.6). Data are very limited for other pain states, which precludes an evidence-based recommendation for broad use of gabapentin to treat all neuropathic pain conditions (Wiffen *et al.* 2017).

Pregabalin. Pregabalin is a novel compound that has analgesic, anticonvulsant, and anxiolytic effects (Shneker and McAuley 2005). In 45 studies involving 11,906 participants, pregabalin at dosages of 300-600 mg/day was effective in improving pain in individuals with postherpetic neuralgia, painful diabetic neuropathy, and mixed or unclassified posttraumatic neuropathic pain. It was not found to improve HIV-related neuropathy (Derry *et al.* 2019). In fibromyalgia specifically, pregabalin at 300-600 mg/day, typically divided into two daily doses, significantly reduced pain for about 1 out of 10 patients over 12-26 weeks with concomitant improvement in quality of life and function (Derry *et al.* 2016). Whereas both pregabalin and gabapentin are FDA approved for neuropathic pain, only pregabalin is approved for fibromyalgia. Pregabalin, gabapentin, and duloxetine have similar efficacy for diabetic neuropathic pain (Quilici *et al.* 2009). The U.S. Drug Enforcement Administration has placed pregabalin in Schedule V of the Controlled Substances Act (indicating a low potential for abuse), possibly because of withdrawal symptoms that were found during clinical trials.

Carbamazepine. A systematic review of 11 trials included 480 participants with trigeminal neuralgia, diabetic neuropathy, and poststroke pain. Overall the quality and quantity of the evidence was low and the duration of the trials was short, at 4 weeks or less. The authors concluded that although carbamazepine is probably effective in some people with chronic neuropathic pain, the current data do not clearly indicate which conditions are most likely to benefit and the risk of adverse events is significant (Wiffen *et al.* 2014). Carbamazepine carries FDA black box warnings for serious dermatological reactions (toxic epidermal necrolysis and Stevens-Johnson syndrome) and aplastic anemia/agranulocytosis.

Other Pharmacological Agents

Tramadol. Tramadol is unique in that it has both opioid and nonopioid effects. It exerts an analgesic effect through m opioid receptor agonism (opioid effect) and weak inhibition of serotonin and norepinephrine reuptake (nonopioid effect). Tramadol is available in both short-and long-acting formulations. The starting dosage for the short-acting formulation is 50 mg once or twice daily, with gradual titration to a maximum of 400 mg/day. The risk of respiratory depression and, presumably, SUD is lower than with other opiates, but tramadol still should be used with caution. Dose reduction is recommended in older adult patients (> 65 years) and in those with renal impairment (creatinine clearance < 30 mL/minute) or cirrhosis of the liver. Multiple trials have demonstrated the efficacy of tramadol in treating pain disorders, including osteoarthritis, fibromyalgia, and neuropathic pain.

A systematic review of the evidence for the use of tramadol in neuropathic pain conditions included six randomized controlled trials (RCTs) involving 438 patients (Duehmke *et al.* 2017). The authors found modest evidence of very low quality that was additionally compromised by risk of bias and concluded that there is inadequate evidence to recommend the use of tramadol in the treatment of neuropathic pain.

A systematic review of tramadol, both alone and in combination with acetaminophen, found that it had little to no important benefit in improvement of mean pain or function in patients with osteoarthritis. High-quality evidence for tramadol's benefit in fibromyalgia is also lacking (Thorpe *et al.* 2018).

Skeletal muscle relaxants. Most skeletal muscle relaxants are approved by the FDA for treating either spasticity (baclofen, dantrolene, and tizanidine) or musculoskeletal pain (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine) (Chou *et al.* 2004). There is insufficient evidence to prove that skeletal muscle relaxants differ in their efficacy, adverse events, or safety. Most trials have focused on acute rather than chronic pain. Cyclobenzaprine is the best-studied muscle relaxant in musculoskeletal disorders overall. In 14 fair-quality trials, it was consistently proven superior to placebo for relieving pain, reducing muscle spasms, and improving functional status (Chou *et al.* 2004). Moreover, 5-mg doses of cyclobenzaprine are just as effective as 10-mg doses (each given three times daily) but cause fewer side effects. Also, 20-mg doses (three times daily) are not more effective than 10-mg doses, and they cause more side effects.

Topical analgesics. A potential advantage of topical agents is avoidance of the systemic side effects often associated with oral medications. Disadvantages are that only localized areas of pain can be effectively treated and that irritating skin reactions occur in a minority of patients. A Cochrane Review summary covering 13 smaller reviews totaling 206 studies and about 30,700 patients found limited efficacy for topical diclofenac and ketoprofen for osteoarthritis and also small benefit for postherpetic neuralgia from high-concentration topical capsaicin. The quality of evidence for other drug preparations and pain conditions was insufficient to support recommendations (Derry *et al.* 2017).

Cannabinoids. The social stigma associated with cannabinoids coupled with political and legal issues related to medical cannabis use have been barriers to research. Increases in the availability of both medical and recreational cannabis products and a more open regulatory environment have renewed interest in the study of these compounds for many conditions, including chronic pain. The presence of specific high-affinity cannabinoid type 1 receptor binding sites has been demonstrated in the CNS and in certain peripheral tissues, whereas cannabinoid type 2 receptors are expressed in high quantities in immune tissues and cells. Two main endogenous cannabinoids have been described, and their role in modulating pain has been increasingly recognized.

There are two FDA-approved cannabinoids (dronabinol and nabilone) for chemotherapy-associated nausea and vomiting and appetite stimulation in wasting illnesses. A review of cannabinoids for chronic pain included 13 different studies evaluating nabiximols, smoked tetrahydrocannabinol (THC), nabilone, THC oromucosal spray, dronabinol, oral THC, and ajuvenic acid capsules. The authors suggested that moderate-quality evidence existed that smoked THC and nabiximols may offer benefit to chronic pain conditions as a whole (Whiting *et al.* 2015). Despite advancements in cannabinoid science, many heterogeneous cannabinoid preparations (both legal and illicit) exist, which makes consistent dosing, potential efficacy, and adverse events rather unpredictable.

Ketamine. Ketamine, an analgesic that is thought to exert its effects via antagonism of *N*-methyl-D-aspartate receptors, also can be used for anesthesia. It has been studied in the treatment of chronic pain, but the quality of evidence remains modest, as described in reviews (Michelet *et al.* 2018; Orhurhu *et al.* 2019). In addition to the lack of high-quality evidence, it has largely been studied in intravenous preparations. Reliable information about the efficacy of oral ketamine in outpatient treatment of chronic pain is lacking. Ketamine may have a place in the standard treatment of chronic pain in the future.

Nonpharmacological Treatments

Psychotherapy and Behavioral Interventions

Nonpharmacological treatments are not discussed in detail but need to be mentioned because of their important role in the management of chronic pain. Medications are typically targeted to symptoms, but dysfunctional beliefs, attitudes, coping styles, and behaviors frequently develop in patients with chronic pain and contribute to its perpetuation and their disability. Pain can lead to depression, anxiety, disability, or loss of social contact. People can develop the view that life has been irreversibly ruined by pain or see their pain as a catastrophe that cannot be overcome The goals of psychological treatment for pain can be broadly placed into four categories: pain, mood, catastrophizing, and disability secondary to pain. Just as in other chronic medical disorders, pharmacotherapy is necessary but not sufficient for optimizing outcomes. A review (Williams *et al.* 2020) including 75 studies of psychological therapies for chronic pain (excluding headache) and 9,401 participants found the largest evidence base favoring the use of cognitive-behavioral therapy over active control or treatment as usual, with the quality of evidence in the moderate to low range. A variety of other behavioral therapies, such as mindfulness meditation variants, biofeedback, hypnosis, music, and art therapy, were included, and reliable benefit was not clearly demonstrated. The authors noted that the quality of evidence in these trials was very low.

Acceptance and commitment therapy was reviewed, and some studies suggested greater benefit for pain in comparison with treatment as usual and reduced disability compared with an active control condition. The authors were careful to "encourage caution when interpreting" this low-quality evidence (Williams *et al.* 2020).

In a separate article (Eccleston and Crombez 2017), an argument was put forward supporting the possibility of benefit existing but being undetectable because of the proliferation of small, poorly designed studies that flood the dataset with noise. Psychologically based therapies have a place in the management of chronic pain and, after one considers possible harms, they should be part of a comprehensive pain management plan. Future studies should focus on producing higher-quality evidence that can better guide future practice.

Exercise

A review of physical activity and exercise that included 21 systematic reviews covering 381 studies and 37,143 participants (Geneen *et al.* 2017) found a dearth of high-quality evidence and rated the quality of evidence overall as low. Nevertheless, exercise is supported as an intervention with few adverse events that may benefit pain severity, physical function, and overall quality of life.

Combination Therapy

The treatment of chronic pain often includes the stepwise addition of medications to a patient's regimen and deletion if a therapy shows no benefit. In addition to medications given to produce analgesia, pain management may include medications to treat the side effects of the analgesics, such as laxatives or stool softeners for patients receiving opioids, gastroprotective medications for those receiving NSAIDs, and psychostimulants to combat excessive somnolence.

Very few studies have tested combinations of treatments to determine their additive value compared with monotherapy. Only limited data suggest that the combination of acetaminophen and NSAIDs has additive pain-relieving effects (Schug 2005). The largest trial (892 community-derived subjects) found greater pain relief with the combination of acetaminophen and ibuprofen than with either drug alone (Doherty *et al.* 2011). More data show a beneficial effect of combining acetaminophen with opioids, including codeine, tramadol, and morphine. Indeed, one of the more common fixed combinations in a single pill has been the coupling of an opioid, such as codeine, tramadol, oxycodone, or hydrocodone, with a nonopioid analgesic such as acetaminophen or aspirin. Caution must be taken to avoid excessive amounts of acetaminophen beyond 4 g/day while escalating dosing when more analgesia is required. Head-to-head clinical trials comparing different analgesics for chronic pain, separately or in combination, are rare, and there is little high-quality evidence available.

When optimal pain relief has not been achieved it is necessary to decide whether to switch to a new treatment or to add to what is currently being provided. Given the paucity of combination drug trials, this decision is guided by practical considerations. Switching to another monotherapy is often less costly than combining two or more treatments and often is done when a patient has had only a minimal response to and/or poor tolerance of the initial treatment. However, adding a second treatment may be favored when there has been at least a partial response to the first therapy or when the second treatment has a different mechanism of action that may complement the original treatment. Factors influencing combination therapy decisions include not only added efficacy but also costs, side effects, adherence, and patient preferences. Sometimes the secondary effects of a drug may influence the decision to use it in a particular patient. For example, the side effect of sedation that occurs with certain medications (e.g., gabapentin or pregabalin) may be troublesome in one patient, whereas in another it may be useful to treat comorbid insomnia. The antidepressant effects of a particular adjunctive pain medication (e.g., an SNRI such as duloxetine) may reduce both pain and mood disturbances in a patient with diabetic neuropathic pain and comorbid major depressive disorder. TCAs could serve the same purpose, although higher dosages of TCAs are typically required for antidepressant action than for analgesic action, in which case the side effects of higher-dose TCAs, especially their cardiovascular effects, must be considered as well.

Selected Pain Disorders

The study and treatment of chronic pain conditions has been hindered by taxonomy and treatment guidelines based on consensus or expert opinion rather than best available evidence. In an effort to address this core problem, the American Pain Society formed a partnership with the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) to undertake the task of creating a systematically implemented and evidence-based taxonomy for chronic pain conditions called the ACTTION-American Pain Society Pain Taxonomy (AAPT). The AAPT separates chronic pain conditions into five major systems: peripheral nervous system and CNS, musculoskeletal system, orofacial and head system, visceral/pelvic/urogenital system, and other disease-associated pain that cannot be classified elsewhere (Fillingim *et al.* 2014).

Neuropathic Pain

The two main categories of neuropathic pain are peripheral neuropathic pain and central neuropathic pain. As indicated by their names, peripheral neuropathic pain results from injury to or dysfunction of the peripheral nerves, and central neuropathic pain results from damage to or dysfunction in the CNS. Peripheral neuropathic pain is commonly caused by diabetes, autoimmune conditions, chemotherapy for cancer, trauma, inherited disorders (e.g., Charcot-Marie-Tooth disease), chronic alcohol use, and other factors. The most common etiologies for central neuropathic pain are multiple sclerosis, poststroke pain, and spinal cord injury (Watson and Sandroni 2016). Overall, chronic neuropathic pain conditions are relatively common, although the range of estimates is wide, from 1% to 17.9% in the general population in a systematic review (van Hecke *et al.* 2014).

A meta-analysis of 229 RCTs evaluating pharmacotherapy for neuropathic pain (Finnerup *et al.* 2015) showed generally modest effects on pain. One hundred twenty-seven (55%) of the 229 trials involved patients with painful diabetic polyneuropathy or postherpetic neuralgia. Pooled NNTs were 6.4 for SNRIs, mainly including duloxetine (seven of nine studies positive) and venlafaxine (two of five studies positive); 7.7 for pregabalin; 7.2 for gabapentin; and 10.6 for capsaicin high-concentration patches. NNTs were lower for TCAs, opioids, tramadol, and botulinum toxin A and were undetermined for lidocaine patches. Tolerability and safety were higher for topical drugs, and costs were lower for TCAs and tramadol. These findings led to the following:

1. A strong recommendation for TCAs, SNRIs, pregabalin, and gabapentin as first-line treatments

2. A weak recommendation for lidocaine patches, capsaicin high-concentration patches, and tramadol as second-line treatments
3. A weak recommendation for opioids and botulinum toxin A as third-line treatments

The IASP noted that "although few clinical trials have been conducted, no medications have demonstrated efficacy in patients with lumbosacral radiculopathy, which is probably the most common type of neuropathic pain" (Dworkin *et al.* 2007, p. 237). Neuropathy related to HIV and cancer chemotherapy may also be more refractory to treatment than other types of neuropathic pain. The IASP also remarked that little is known regarding the treatment response of those with mild to moderate neuropathic pain because most trials have enrolled patients with more severe neuropathic pain. Moreover, long-term effectiveness is unknown because most RCTs have been of less than 3 months' duration. The IASP also favored secondary amine TCAs (nortriptyline and desipramine) over tertiary amine TCAs (amitriptyline and imipramine) because of their comparable efficacy but fewer side effects. Finally, the IASP concluded that the magnitude of pain reduction associated with opioid analgesics is at least as great as that obtained with other treatments for neuropathic pain.

Central neuropathic pain syndromes may respond differently to pharmacotherapy. Some evidence suggests benefit from lamotrigine and amitriptyline for central poststroke pain, pregabalin and lamotrigine are favored for spinal cord injury, and duloxetine and cannabinoids show some promise for central neuropathic pain due to spinal cord injury (Watson and Sandroni 2016).

Duloxetine, venlafaxine, pregabalin, oxcarbazepine, TCAs, gabapentin, and botulinum toxin have been found to be more effective than placebo for diabetic neuropathic pain (Waldfogel *et al.* 2017; Wiffen *et al.* 2017). Combination therapy using medicines with different mechanisms of action is used clinically, but high-quality evidence supporting specific approaches is lacking.

Fibromyalgia

Mechanisms and Evaluation

Fibromyalgia is one of the most common musculoskeletal disorders seen in rheumatology practice as well as primary care. It is often classified among the functional somatic syndromes, which include irritable bowel syndrome, chronic fatigue syndrome, temporomandibular joint disorder, interstitial cystitis, and other symptom-based conditions manifested by a cluster of symptoms for which the pathophysiological mechanism is not well understood (Aaron and Buchwald 2001).

The American College of Rheumatology core diagnostic criteria for fibromyalgia, initially developed in 2010 and revised in 2016 (Wolfe and Hauser 2011; Wolfe *et al.* 2016), depend entirely on clinical history and exam and do not require any laboratory or radiological testing. According to the American College of Rheumatology, fibromyalgia may be diagnosed when *all* of the following four criteria are met:

1. Generalized pain, defined as pain in at least four of five regions, is present.
2. Symptoms have been present at a similar level for at least 3 months.
3. Widespread pain index is > 7 and symptom severity scale score is > 5, or widespread pain index is 4-6 and symptom severity scale score is > 9.
4. A diagnosis of fibromyalgia is valid irrespective of other diagnoses and does not exclude the presence of other clinically important illnesses.

Another set of criteria have been proposed as part of the AAPT with a focus on providing a practical basis for clinical work and also good diagnostic validity for trial inclusion to help reduce heterogeneity in studies, in turn aspiring to higher-yield data (Arnold *et al.* 2019). AAPT core diagnostic criteria for fibromyalgia are as follows:

1. Multisite pain defined as six or more pain sites out of a total of nine possible sites
2. Moderate to severe sleep problems *or* fatigue

3. Multisite pain plus fatigue or sleep problems present for at least 3 months

The AAPT Fibromyalgia Work Group also identified a set of common associated features that are not necessary for but may support a diagnosis of fibromyalgia. They are tenderness, dyscognition (concentration problems, forgetfulness, disorganized or slow thinking), musculoskeletal stiffness, and environmental sensitivity or intolerance.

The prevalence of fibromyalgia is estimated at between 0.5% and 12%, and the condition is more common in women than in men, at an approximately 3:1 ratio (Arnold *et al.* 2019). The prevalence rises with age around 50-59 years, then declines in older age around 80 years. The average age at onset is between 30 and 50 years, but fibromyalgia has been noted to occur in children and adolescents, with an estimated prevalence between 1% and 6.2%.

The pathogenesis of fibromyalgia is unclear, but one putative mechanism relates to a centralized pain state that could be considered a single, lifelong disease that manifests in a variety of pain states, including headaches, temporomandibular joint disorder, chronic fatigue, irritable bowel syndrome, and other regional pain syndromes that are poorly understood. A family history of chronic pain is often present. Early life adverse events, trauma, medical illness, and psychosocial stressors are risk factors for developing fibromyalgia.

The primary problem in fibromyalgia appears to be not that there is too much input coming from the pressure nociceptors peripherally but rather that there is inadequate filtering of that activity, perhaps because of decreased activity of descending anti-nociceptive pathways. In fact, multiple mechanisms seem to be operative in fibromyalgia (Abeles *et al.* 2007). Two key mechanisms are as follows:

1. Functional imaging studies in fibromyalgia patients have shown increased blood flow to pain-relevant areas of the brain at lower

thresholds of nociceptive input.

2. There appears to be dysregulation of descending inhibitory pain pathways. Thus, the pain "amplifier" is turned up and the "mute" button is turned down in fibromyalgia patients. This concept is known as *central sensitization* (Bourke *et al.* 2015).

Table 59-3 summarizes the current state of evidence on fibromyalgia.

TABLE 59-3. Evidence-based fibromyalgia treatments from three national guidelines

	Strength of recommendation[a]		
Treatment	**Canada**	**Israel**	**Germany**
Pharmacotherapy			
TCAs (e.g., amitriptyline)	A	A	B
SNRIs (duloxetine, milnacipran)	A	A	B/C
a_2d ligands (pregabalin, gabapentin)	A	A	C
Tramadol	C	B	--
SSRIs	A	--	C
Nonpharmacological therapies			
Cognitive-behavioral therapy	A	A	A
Exercise (aerobic)	A	A	A
Balneotherapy (spas, hydrotherapy)	--	C	B

Note. SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; -- = not applicable.

[a] A = should be offered to most patients; B = may be offered to most patients but may not be offered to a substantial minority; C = can be offered to a minority of patients.

Source. Adapted from Ablin *et al.* 2013.

Low Back Pain

A systematic review by Chou *et al.* (2017) provides a comprehensive update on the evaluation and management of low back pain. Most low back pain (85%) is nonspecific--that is, it cannot be attributed to a specific disease or spinal abnormality. Classification schemes frequently conflict with one another, and there is little evidence that labeling patients by using specific anatomical diagnoses improves outcomes. In a primary care setting, low back pain is only occasionally caused by a specific serious disorder, such as cancer (0.7% of cases), compression fracture (4%), or spinal infection (0.01%). The estimated prevalence of ankylosing spondylitis in primary care patients ranges from 0.3% to 5%. Spinal stenosis and symptomatic herniated disc are present in about 3% and 4% of patients, respectively. Cauda equina syndrome, due to massive midline disc herniation, is very rare, found in 0.04% of patients with low back pain. Table 59-4 outlines some key recommendations with respect to the evaluation and management of low back pain. In the absence of red flags, a conservative approach for at least 4 weeks is usually warranted, even if sciatica is present.

TABLE 59-4. Key aspects of the evaluation and management of low back pain

Most back pain (> 70%-80%) improves in the first 2-6 weeks. Thus, a 4-week wait (i.e., a conservative approach) is warranted (even with sciatica) in the absence of red flags.

Red flags that may prompt earlier diagnostic testing or referral include the following:

* Cancer: history of cancer (strong predictor) or unexplained weight loss, failure to improve after 4 weeks, and age greater than 50 years (all weaker predictors)
* Infection (vertebral): fever, intravenous drug use, recent infection (none well studied)

Note. ESR = erythrocyte sedimentation rate; NSAID = nonsteroidal antiinflammatory drug; TCA = tricyclic antidepressant.

* Compression fracture: older age, osteoporosis, steroid use

* Cauda equina syndrome rare (0.04%), urinary retention 90% sensitive

Diagnostic tests are needed in only a minority of cases (with red flags or persistent neurological signs):

* MRI is the preferred imaging study (less radiation and better visualization of soft tissue, vertebral marrow, and the spinal canal).

* With some weaker red flags (e.g., age > 50 years), plain films and ESR may be obtained first and MRI obtained only if the findings on these tests are abnormal or symptoms persist.

Psychological factors are a stronger predictor of chronicity and functional outcomes such as disability than physical exam findings or the severity or duration of pain.

No treatment for back pain has good-quality (grade A) evidence of substantial benefit. The following have fair-quality (grade B) evidence of moderate benefit or small benefit but no significant harm, costs, or burdens:

* Pharmacotherapy: acetaminophen, NSAIDs, TCAs, tramadol/opiates, benzodiazepines

* Nonpharmacological treatments: chiropractic, acupuncture, massage, yoga, exercise, progressive relaxation, cognitive-behavioral therapy, intensive interdisciplinary rehabilitation

Note. ESR = erythrocyte sedimentation rate; NSAID = nonsteroidal antiinflammatory drug; TCA = tricyclic antidepressant.

Psychological factors are stronger predictors of low back pain treatment outcomes than either physical examination findings or the severity or duration of pain. Psychosocial factors that may predict poorer low back pain outcomes include the presence

of depression, passive coping strategies, job dissatisfaction, higher disability levels, disputed compensation claims, and somatization.

Pharmacotherapy trials for low back pain have been extensively studied, and overall limited benefit has been seen for most typical analgesics. Table 59-4 summarizes the current state of the evidence.

Osteoarthritis

Osteoarthritis is one of the most common musculoskeletal pain disorders in both primary care and specialty settings. Its prevalence typically increases with age (particularly after age 50 years), with the majority of individuals older than 65 years having at least one joint affected. Joints commonly involved in osteoarthritis include the distal and proximal interphalangeal (but not metacarpal) joints of the fingers, the base of the thumb, the knees, the hips, and the cervical and lumbar regions of the spine. The shoulder and elbow are rarely involved. The most common finding on physical examination is an increase in joint size secondary to osteophyte formation. Plain radiographs are typically the only diagnostic test required to confirm a diagnosis of osteoarthritis, which is manifested by loss of joint space and/or osteophyte formation.

Unlike with rheumatoid arthritis and other inflammatory arthritides, the structural changes in osteoarthritis are not amenable to specific disease-modifying treatments. The focus of treatment for osteoarthritis is a reduction in pain and preservation of function. NSAIDs are the mainstays of pharmacotherapy (Towheed *et al.* 2006). Although acetaminophen has traditionally been widely used to treat osteoarthritis, the evidence shows only modest benefits over placebo, and the status of acetaminophen as a first-line treatment for osteoarthritis is in question (Leopoldino *et al.* 2019).

Low-quality evidence suggests that chondroitin, either alone or in combination with glucosamine, is superior to placebo for the treatment of osteoarthritis pain in short-term studies (Singh *et al.* 2015). In contrast, hyaluronic acid seems to be effective in knee osteoarthritis, although it does require intra-articular administration. It also seems to be similar in efficacy to continuous NSAID therapy (Bannuru *et al.* 2014) and intra-articular corticosteroids (Bannuru *et al.* 2009). The long-term use of opioids for the treatment of pain related to osteoarthritis of the hip and knee confers benefits that are small at best and carries significant risks of side effects (da Costa *et al.* 2014).

In contrast to the many trials of antidepressants for neuropathic pain, fibromyalgia, and chronic low back pain, few studies have investigated antidepressants for the treatment of osteoarthritic pain. One exception is duloxetine, for which three trials in osteoarthritis have shown efficacy for pain (Pergolizzi *et al.* 2013). When depression co-occurs with arthritis, it can explain as much of the variance in pain intensity as the objective severity of the arthritis (Katon *et al.* 2007), and RCTs have shown that treating depression in arthritis patients may reduce pain as well as depression (Kroenke *et al.* 2009a; Lin *et al.* 2003). Thus, although antidepressants cannot currently be recommended as a first-line treatment for osteoarthritis patients without depression, screening for and co-managing depression may benefit pain outcomes.

Headache

Although there are less common and/or more serious causes of headache, most individuals with chronic headache have either migraine headache or tension-type headache (TTH). Up to one-third of the general population report TTH, and 10% experience migraine headaches (Robbins and Lipton 2010). Patients with migraine headache present to physicians for care more often than those with TTH. Sinus disease, hypertension, and eye strain are not common causes of headache, contrary to common lore.

Migraine is easier to diagnose in the presence of auras, which most commonly include a visual prodrome such as blind spots (scotomas), zigzag patterns (fortification spectra), or flashing lights (scintillae). However, auras occur in less than 20% of patients with migraine attacks.

Diagnostic criteria can differentiate migraine headache from TTH. Migraine without aura is diagnosed if at least two of the following are true: 1) nausea is present during the attack, 2) light sensitivity is present during the attack, and 3) some of the attack interferes with the patient's activities. TTH is diagnosed if the headache is not associated with nausea and at least two of the following are true: 1) the headache is bilateral, 2) non-pulsatile pain is present, 3) the pain is mild to moderate in intensity, and 4) the headache is not worsened by activity.

Some individuals with migraine or TTH develop chronic daily headache, defined as a headache frequency of [?] 15 days a month for longer than 3 months. A common reversible cause of chronic daily headache is medication overuse headache, which can develop when analgesics are taken for headaches more than 2-3 days per week. All analgesics have the potential for medication overuse headache, but the risk appears to be the highest with opioids or combination analgesics containing butalbital or caffeine, intermediate with triptans, and lowest with NSAIDs. Medication overuse headache often manifests as a headache that is present on awakening and that responds to analgesics with only transient relief. This can lead to a problematic cycle of increased analgesic use.

Neuroimaging is low yield in headache evaluation. Even among selected patients with headache seen in tertiary referral centers, less than 1%-2% have abnormal imaging findings that influence treatment (Clarke *et al.* 2010). Factors that may justify an imaging study are focal neurological signs or symptoms, onset of headache after age 40 years, and severe or worsening headaches that do not respond to appropriate therapy.

An initial stepped-care approach to pharmacotherapy for migraine and TTH is summarized in Table 59-5. Treatment of less common types of headache (e.g., cluster headache) or chronic refractory headache warrants referral to a neurologist or other headache specialist.

TABLE 59-5. Stepped-care pharmacotherapy for headache

Medication	**Migraine**	**Tension type**
Acute (abortive)		
Step 1	NSAID	Acetaminophen or NSAID
Step 2	Triptan	
Step 3	Opioid	

Note. NSAID = nonsteroidal antiinflammatory drug.
Source. Derived from Becker *et al.* 2015; Loder *et al.* 2012.

Medication	Migraine	Tension type
Prophylactic (preventive)		
Step 1	Beta-blocker	Amitriptyline or nortriptyline
Step 2	Topiramate	
Step 3	Divalproex	

Note. NSAID = nonsteroidal antiinflammatory drug.
Source. Derived from Becker *et al.* 2015; Loder *et al.* 2012.

Algorithmic Approach to the Treatment of Chronic Pain

This chapter has focused on the main classes of treatments for chronic pain, with a particular emphasis on pharmacotherapy. Five of the most common pain disorders have been discussed: neuropathic pain, fibromyalgia, low back pain, osteoarthritis, and headache. On the basis of our reviews within these parameters, an evidence-based stepped-care algorithm for treating pain is summarized in Table 59-6. This algorithm is adapted from a previous review (Kroenke *et al.* 2009b) and was tested (in an earlier version) in a clinical trial (Kroenke *et al.* 2014).

TABLE 59-6. Evidence-based stepped-care analgesic algorithm by type of pain condition

Step	Medication	Dosing	MSK[a]	FM	NP	HA
1	**Simple analgesics**					
	Acetaminophen	650-1,000 mg every 6 h (maximum 3,000-4,000 mg/day, but only 2,000 mg/day if cirrhosis or [?] 3 alcoholic drinks/day)	+	+	+	+

Step	Medication	Dosing	MSK[a]	FM	NP	HA
	NSAIDs[b,c]					
	Naproxen	500 mg every 12 h or 500 mg in A.M. and then 250 mg bid (up to 1,000 mg/day)	+	+	+	+
	Ibuprofen	600 mg every 6 h (maximum 2,400 mg/day)	+	+	+	+
	Salsalate	1,000 mg every 8 h or 1,500 mg every 12 h (up to 3,000 mg/day)	+	+	+	+
	Meloxicam	7.5-15 mg/day (up to 15 mg/day)	+	+	+	+
	Etodolac	300 mg every 8 h or 500 mg every 12 h (maximum 1,000 mg/day)	+	+	+	+
	Diclofenac	50 mg every 8 h (maximum 150 mg/day)	+	+	+	+
	Sulindac	150-200 mg bid (maximum 400 mg/day)	+	+	+	+
2	**TCAs[b]**					
	Amitriptyline	Start at 10-25 mg/day; titrate to 100 mg/day		+	+	+-
	Nortriptyline	Start at 10-25 mg/day; titrate to 100 mg/day		+	+	+-

Step	Medication	Dosing	MSK[a]	FM	NP	HA
2	**Muscle relaxants[b]**					
	Cyclobenzaprine	5-10 mg bid to tid (maximum 20-30 mg total daily dose)	+	+-		
	Methocarbamol	Start at 500 mg qid; can increase to 1,000 mg qid	+-	+-		
	Tizanidine	Start at 2 mg tid; can increase to 6-8 mg tid				
2	**Gabapentoids**					
	Gabapentin	Start at 100 mg tid; titrate to 900-1,200 mg tid		+-	++	+-
	Pregabalin	Start at 75-100 mg bid; titrate to 450 mg/day total in twice-daily doses		++	++	
2	**SNRI antidepressants**					
	Venlafaxine	Start at 75 mg/day sustained release; titrate to 225 mg/day		+-	+-	+-
	Duloxetine	Start at 30 mg/day; titrate to 60 mg/day	+	++	++	
	Milnacipran	Start at 12.5 mg bid; titrate to 50 mg bid		++		
3	**Category IV controlled**					
	Tramadol	Start at 25 mg bid or tid; titrate to maximum 100 mg qid	+	+	+	+

Step	Medication	Dosing	MSK[a]	FM	NP	HA
4	**Category II opiates[b]**					
	Hydrocodone	Start at 5 mg bid to qid; try to keep [?] 10-20 mg qid	+-		+-	+-
	Oxycodone	Start at 5 mg bid to qid; try to keep [?] 10-20 mg qid (a sustained-release formulation is also available that can be given twice daily)	+-		+-	
	Morphine	Start at 15 mg bid sustained release; try to keep [?] 60 mg bid	+-		+-	
A	**Migraine-specific agents[b,d]**					
	Triptans[b]					
	Sumatriptan	50-100 mg oral or 5-20 mg nasal spray				+
	Zolmitriptan	2.5-5.0 mg oral or nasal spray				+
	Beta-blockers[b]					
	Propranolol	20-80 mg bid				+
	Metoprolol	25-100 mg bid				+
	Topiramate	Start at 25 mg hs to bid; titrate to 50 mg bid (or 100 mg hs)				+
	Divalproex	Start at 250 mg bid; titrate to				+

Step	Medication	Dosing	MSK[a]	FM	NP	HA
		500 mg bid				
B	**Topical analgesics**					
	Capsaicin	Apply 0.025%-0.075% cream 2-4 times/day over painful area	+		+	
	Lidocaine gel or patch	Gel or ointment 2-4 times/day or 5% patch ([?] 3 patches/day)	+		+	
	Salsalate/other NSAIDs	Apply 2-4 times/day over painful area	+		+	

Note. FM = fibromyalgia; HA = headache; MSK = musculoskeletal; NP = neuropathic; NSAID = nonsteroidal antiinflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

++ = FDA approved and/or strong evidence from multiple randomized controlled trials; + = moderate evidence; +- = mixed (inconclusive) evidence.

[a] Includes back pain, osteoarthritis, and other localized joint or musculoskeletal pain.

[b] This is not a list of all drugs in this class.

[c] Consider trials of at least two NSAIDs; over-the-counter = naproxen, ibuprofen, ketoprofen.

[d] Triptans used for acute migraine treatment; other drugs used for migraine prevention.

Source. Chou *et al.* 2017; Kroenke *et al.* 2009b; 2014.

Other Issues

Treatment of Pain in the Context of Depression or Anxiety

There is substantial evidence that people with pain and depression have significantly reduced physical, mental, and social function compared with people with only pain or depression (IsHak *et al.* 2018). In particular, the presence of pain negatively affects depression outcomes, and depression in turn makes pain treatments less effective. Anxiety may have a similar effect, although the research in this area is less substantial than for depression. Several trials have shown that depression treatment also benefits patients on pain outcomes and that simultaneous treatment of comorbid depression and pain is effective (Greco *et al.* 2004; Kroenke *et al.* 2009a; Lin *et al.* 2003).

Given the high co-occurrence of pain with anxiety and depression, practitioners should screen all pain patients for symptoms of anxiety and depression. It is also prudent to identify and treat pain problems when treating anxiety or depression, as untreated pain will likely limit the improvement in psychiatric symptoms.

Antidepressant selection may be influenced by the presence of pain. TCAs and SNRIs appear to be more effective than SSRIs or other antidepressants in patients with comorbid pain.

Placebo Effect

As with other symptom-based conditions (e.g., depression, anxiety, somatoform disorders), pain has a placebo response in the range of 30%-40% or higher. This can make it challenging to separate the specific effects of a pain treatment--medication or nonpharmacological treatment--from placebo or other nonspecific effects. At the same time, placebo effects on pain outcomes can be useful in clinical practice, including in terms of patient expectancy for an analgesic outcome and the clinical benefits of a positive therapeutic relationship.

Experimental work has revealed some interesting physiological effects of placebo. A meta-analysis of 12 studies (1,183 participants) was conducted to examine the effects of placebo and an opioid antagonist, naloxone, on pain (Sauro and Greenberg 2005). Placebo administration was associated with a decrease in self-reported pain, and a hidden or blind injection of naloxone reversed placebo-induced analgesia. An experimental study in 20 healthy subjects found that placebo and nocebo effects (i.e., the therapeutic and adverse effects, respectively, of inert substances or sham procedures) are associated with opposite responses of dopaminergic and endogenous opioid neurotransmission in a distributed network of regions throughout the brain (Scott *et al.* 2008). The results support other literature showing that the belief in and expectation of analgesia induce discrete physiological changes, leading to relief from pain, and this response may be mediated by endogenous opioids.

Clinical ways to take advantage of the placebo effects of an analgesic were summarized by Klinger *et al.* (2014):

- **Enhancing expectations**--examples include 1) emphasizing positive drug effects and avoiding an overemphasis on side effects, 2) explaining the mechanism of drug action, 3) having personal interaction rather than using only written materials, and 4) explaining the course of drug action while avoiding unrealistic promises.
- **Enhancing learning components**--examples include 1) focusing on sensory aspects of a pain medicine, such as its color or size, to distinguish it from other medicines the patient may be taking; 2) associating analgesic medication with positive internal states and positive external conditions; 3) combining analgesic intake with other pain-relieving techniques; and 4) encouraging time-contingent (scheduled) rather than pain-contingent (intermittent) use of analgesics.

Gaps in the Knowledge Base Regarding the Treatment of Chronic Pain

There are several important gaps in knowledge regarding treatment that in fact are probably not unique to chronic pain. For one thing, there are few head-to-head trials, which limits our ability to compare various active treatments against each other. Few trials have evaluated different strategies for choosing initial treatment, so deciding between first-line and subsequent treatments is more a matter of expert consensus, clinician experience, and patient preferences. Evidence is sparse on the effectiveness of dual-medication or other combination therapy versus monotherapy or sequential treatment, even though patients are frequently prescribed more than one medication or treatment. Finally, most treatment trials are short, so evidence of benefits sustained beyond 4-12 weeks is often lacking. This is a critical gap when the clinical entity being investigated is defined by long-term persistence.

Despite these gaps, substantial evidence has accumulated for treating chronic pain. Avoiding ineffective treatments and maximizing the use of treatments proven beneficial in clinical trials are likely to produce better outcomes than have often been experienced by clinicians and patients in the management of chronic pain.

Conclusion

Chronic pain remains one of the most complex, prevalent, and morbid medical problems. It occurs across many medical diagnoses and may also exist in situations where the etiology of the pain is unclear. We have a wide variety of tools at our disposal to address chronic pain, including medications, surgical interventions, electrophysiological devices, lifestyle and behavioral approaches, and psychological interventions. Given the complexity of both the clinical condition of chronic pain and the interventions used to treat it, judicious use of these tools must be undertaken to achieve the best results while minimizing side effects and complications of treatment. Clearly, much remains to be discovered about how chronic pain arises and what can be done to eliminate it.

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CHAPTER 60

Treatment of Child and Adolescent Disorders

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This chapter focuses on the use of psychopharmacology for treating psychiatric disorders in children and adolescents. It is important for clinicians to be aware of the evidence base for the use of psychotropic medications by children and adolescents. In this chapter, data from the literature, with a focus on controlled studies, are presented. On the basis of these findings, clinical recommendations regarding pharmacotherapy for childhood psychiatric disorders are offered. The appendix and tables at the end of this chapter contain specific information about dosages, monitoring, and adverse effects of psychotropic medications in pediatric patients.

Psychotropic Medication for Children and Adolescents

Evaluation

Before the initiation of psychotropic medication for children and adolescents, a comprehensive evaluation is necessary to ensure the accuracy of the diagnosis. A thorough history and careful attention to the clinical presentation are central components of the evaluation. The clinician should interview the child and parents separately so that both have the opportunity to freely express their concerns. Extended family members, school personnel, and school records are other potential sources of information.

Clinicians must be skilled at differential diagnosis of childhood psychiatric disorders, given that there is a significant overlap of symptoms between these disorders.

Knowledge of commonly occurring comorbid disorders is also necessary. Medical conditions should be considered within the differential diagnosis and adequately assessed.

Disorder-specific rating scales completed at baseline and during the course of treatment may be useful in the measurement of clinical outcome.

Clinical Issues Affecting Response to Pharmacotherapy

Whenever a child does not respond to initial pharmacotherapy, several clinical issues should be addressed before alternative or adjunctive medication is initiated.

Diagnostic Accuracy

The diagnosis should be reassessed. Often there is symptomatic overlap between disorders that may lead to misdiagnosis. For example, symptoms of excessive energy and distractibility are common features of both ADHD and bipolar disorder.

Comorbid Disorders

Unrecognized comorbid disorders may adversely affect treatment outcome. As an example, comorbid ADHD may lower response rates in the treatment of bipolar disorder (Pavuluri *et al.* 2006).

Psychosocial Factors

Child abuse, domestic violence, family conflict, parental psychopathology, and bullying by peers may lead to symptoms that mimic or exacerbate a preexisting psychiatric disorder.

Medication Compliance

Some children and adolescents are reluctant to take medication because of such reasons as denial of illness, perceived stigma, and side effects. For increased medication compliance, the child or adolescent, as well as the parents, must understand the youth's disorder, course of illness, and goals of treatment. It is important for parents to participate in monitoring their child's medication compliance.

Nonpharmacological Treatment

Psychotherapy may be beneficial, either alone or in conjunction with medication. Specific psychotherapies have been found to be effective in the treatment of some childhood disorders. For example, cognitive-behavioral therapy (CBT) and interpersonal therapy have demonstrated efficacy in the treatment of adolescents with depression (Weersing *et al.* 2017). Similarly, CBT is commonly used for the treatment of childhood anxiety disorders (Wang *et al.* 2017). Behavioral intervention has led to improvement in symptoms of ADHD for children (Coles *et al.* 2020). Family-focused therapy with medication treatment has shown benefit in the treatment of children with bipolar disorder (Miklowitz and Chung 2016). Social skills training can be a useful component of treatment in autism spectrum disorder (Dekker *et al.* 2019).

Informed Consent

Informed consent is necessary before psychotropic medication is prescribed to any patient, but it is particularly important in pediatric psychopharmacology because few medications have been approved by the FDA for young populations. There are five recommended components of informed consent for prescribing psychotropic medications to children and adolescents (Popper 1987). The child's parent(s) and the child or adolescent should be provided with the following information:

1. The purpose (benefits) of the treatment
2. A description of the treatment process
3. An explanation of the risks of the treatment, including risks that would ordinarily be described by the psychiatrist and risks that would be relevant to making the decision
4. A statement of alternative treatments, including nontreatment
5. A statement that there may be unknown risks associated with these medications (This is particularly essential for children because of the paucity of information on the potential long-term effects of psychotropic medications.)

Evidence Base

It is important for clinicians to be aware of the evidence base for medication treatment of each childhood psychiatric disorder. Clinical treatment guidelines generally rely on the strength of the available data in determining first-line agents. In most cases, clinicians should select a medication within the group of first-line agents when initiating medication treatment with a child. Additional factors that will dictate medication choice are prior medication history, medical history, side-effect profile of the drug, and adolescent and parent preferences.

Major Depressive Disorder

The lifetime prevalence of major depressive disorder (MDD) or persistent depressive disorder in adolescents is 11.7% (Merikangas *et al.* 2010). DSM-5 (American Psychiatric Association 2013) criteria are used to establish a diagnosis of MDD in children and adolescents. The mean length of an episode of MDD in youth ranges from 8 to 13 months, and relapse rates range from 30% to 70% (Birmaher *et al.* 2002). There is increasing evidence for the continuity of depression from youth into adulthood (Melvin *et al.* 2013).

Selective Serotonin Reuptake Inhibitors

For the acute and maintenance treatment of MDD in children and adolescents, the FDA has approved two selective serotonin reuptake inhibitor (SSRI) medications: fluoxetine for patients ages 8 years and older and escitalopram for patients ages 12 years and older. Other SSRIs that have been studied in controlled trials for children and adolescents with MDD include citalopram, sertraline, and paroxetine. Information about dosages, monitoring, and adverse effects of SSRIs is provided in the appendix to this chapter.

Fluoxetine

There have been three positive controlled medication trials of fluoxetine in the treatment of MDD in children and adolescents. In the first study, 96 child and adolescent

outpatients (ages 8-17 years) with MDD were randomly assigned to receive fluoxetine 20 mg/day or placebo for an 8-week trial (Emslie *et al.* 1997). The fluoxetine group, with 27 youths (56%) much or very much improved, showed statistically significantly greater improvement in Clinical Global Impression (CGI) Scale scores than the placebo group, with 16 youths (33%) much or very much improved. Medication side effects leading to discontinuation in the study were manic symptoms in three patients and severe rash in one patient.

In a double-blind, placebo-controlled multicenter study of fluoxetine, 219 child and adolescent outpatients (ages 8-17 years) with MDD were randomly assigned to fluoxetine 20 mg/day or placebo for an 8-week trial (Emslie *et al.* 2002). Improvement in depression was statistically significantly greater for the fluoxetine group, as assessed by means of the Children's Depression Rating Scale-Revised (CDRS-R), than for the placebo group. Fifty-two percent of patients treated with fluoxetine were rated as much or very much improved, compared with 37% of patients in the placebo group. Headache was the only side effect that was reported more frequently in the group treated with fluoxetine than in the placebo group.

In a multicenter trial of 439 adolescent outpatients with a diagnosis of MDD (March *et al.* 2004), patients were randomly assigned to receive 12 weeks of fluoxetine (10-40 mg/day), fluoxetine (10-40 mg/day) with CBT, CBT alone, or placebo. Compared with placebo, the combination of fluoxetine with CBT was significantly superior, according to changes in CDRS-R scores. Combination treatment with fluoxetine and CBT was significantly superior to treatment with fluoxetine alone or CBT alone. Fluoxetine monotherapy was superior to CBT. Response rates (defined as CGI ratings of much or very much improved) were 71% for fluoxetine-CBT combination therapy, 61% for fluoxetine, 43% for CBT, and 35% for placebo.

Escitalopram

There have been two controlled trials of escitalopram in the treatment of youth with depression, one positive and one negative. The efficacy of escitalopram in adolescents was demonstrated in a double-blind, placebo-controlled multicenter trial of 157 adolescents with MDD (Emslie *et al.* 2009). Patients were randomly assigned to escitalopram (dosage range = 10-20 mg/day) or placebo for an 8-week trial. The group treated with escitalopram showed statistically significantly greater improvement in depression (CDRS-R scores) than the placebo group. Sixty-four percent of escitalopram-treated patients were much or very much improved, compared with 53% of placebo-treated patients. In a study that included 264 children and adolescents with MDD (Wagner *et al.* 2006a), there was no significant difference in improvement on CDRS-R scores at endpoint between escitalopram and placebo. The most common adverse events with escitalopram were headache, abdominal pain, nausea, insomnia, and menstrual cramps.

Citalopram

There have been two controlled trials of citalopram in the treatment of depression in youth, one with positive and one with negative results. The efficacy of citalopram was demonstrated in a double-blind, placebo-controlled multicenter trial of 174 outpatient children and adolescents (ages 7-17 years) with MDD (Wagner *et al.* 2004b). Patients were randomly assigned to receive citalopram (dosage range = 20-40 mg/day; mean daily dosage = 23 mg for children, 24 mg for adolescents) or placebo for an 8-week trial. Compared with the placebo group, the citalopram group showed statistically significantly greater improvement in depression (CDRS-R scores). The most common adverse events were headache, nausea, rhinitis, abdominal pain, and influenza-like symptoms. A European double-blind, placebo-controlled multicenter study (von Knorring *et al.* 2006) of citalopram for 224 adolescents with MDD failed to show superiority of citalopram to placebo on the primary efficacy measures--the Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present Episode Version (K-SADS-P) and the Montgomery-Asberg Depression Rating Scale (MADRS). The most commonly reported adverse events were headache, nausea, and vomiting.

Sertraline

The efficacy of sertraline for MDD was evaluated in two identical double-blind, placebo-controlled multicenter studies of 376 outpatient children and adolescents (Wagner *et al.* 2003a). Patients were randomly assigned to sertraline (dosage range = 50-200 mg/day; mean daily dosage = 131 mg) or placebo for a 10-week trial. Compared with the placebo group, the group receiving sertraline showed a statistically significantly greater improvement in depression (CDRS-R scores). Response rates (decrease [?] 40% in baseline CDRS-R scores) were 69% in the group treated with sertraline and 59% in the placebo group. The most common side effects in the group treated with sertraline were headache, nausea, insomnia, upper respiratory tract infection, abdominal pain, and diarrhea.

Sertraline, CBT, and combined CBT plus sertraline were compared in the treatment of 73 adolescents with depressive disorders (Melvin *et al.* 2006). All treatments resulted in statistically significant improvement on all outcome measures; there were no significant advantages of combined treatment.

In the Adolescent Depression and Psychotherapy Trial (ADAPT [Goodyer *et al.* 2008]), 208 adolescents with MDD were randomly assigned to receive an SSRI alone or an SSRI plus CBT for 12 weeks. No significant differences were found between the groups; 44% of the SSRI-alone group and 42% of the SSRI-plus-CBT group were much or very much improved on the CGI-Improvement subscale (CGI-I).

Paroxetine

There have been three double-blind, placebo-controlled trials of paroxetine for treatment of depression in children and adolescents, all of which had negative findings on the primary outcome measure. In a study of 275 adolescent outpatients (ages 12-18 years) with MDD, patients were randomly assigned to paroxetine (dosage range = 20-40 mg/day; mean daily dosage = 28 mg), imipramine (dosage range = 200-300 mg/day; mean daily dosage = 205 mg), or placebo for an 8-week trial (Keller *et al.* 2001). There was no statistically significant difference between treatment groups on the primary efficacy measure of reduction in total score on the Hamilton Rating Scale for Depression. The most common side effects reported for paroxetine were headache, nausea, dizziness, dry mouth, and somnolence.

Two hundred six children and adolescents (ages 7-17 years) with MDD were included in an 8-week double-blind, placebo-controlled, randomized multicenter study of paroxetine treatment (Emslie *et al.* 2006). There was no statistically significant difference

between patients treated with paroxetine and those given placebo on change from baseline in CDRS-R total score at endpoint. Adverse events reported with paroxetine with an incidence greater than 5% and at least twice that with placebo were dizziness, cough, dyspepsia, and vomiting.

A 12-week international placebo-controlled multicenter trial of paroxetine in 286 adolescents with MDD failed to show superiority for paroxetine compared with placebo on change from baseline in MADRS or Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Lifetime Version total score (Berard *et al.* 2006).

Other Antidepressants

Information about dosages, monitoring, and adverse effects of commonly used antidepressants are provided in the appendix to this chapter.

Venlafaxine

Two double-blind, placebo-controlled multicenter studies have evaluated the efficacy of venlafaxine extended release (XR) in the treatment of MDD in 165 and 169 child and adolescent outpatients, respectively (Emslie *et al.* 2007). Patients were randomly assigned to venlafaxine XR (37.5-225 mg/day; flexible dosage based on body weight) or placebo for 8-week trials. Both studies were negative on the primary outcome measure of change from baseline to endpoint in the CDRS-R scores. The most common adverse events with venlafaxine were anorexia and abdominal pain (Emslie *et al.* 2007).

Nefazodone

There have been two double-blind, placebo-controlled multicenter trials of nefazodone in the treatment of MDD in youth (Rynn *et al.* 2002; U.S. Food and Drug Administration 2004b). These studies failed to find statistically significant differences in improvement in baseline-to-endpoint CDRS-R scores between the nefazodone-treated group and the placebo-treated group. The most common adverse events with nefazodone were headache, abdominal pain, nausea, vomiting, somnolence, and dizziness.

Bupropion

There are no controlled trials of bupropion for the treatment of pediatric depression. In an 8-week study of bupropion sustained release (dosage range = 100-400 mg/day; mean daily dosage = 362 mg) in the treatment of

11 adolescents with MDD, 8 adolescents (79%) showed a 50% reduction in depression scores from baseline (Glod *et al.* 2000). Bupropion sustained release was assessed in an 8-week open study for the treatment of comorbid depression and ADHD in 24 adolescents (Daviss *et al.* 2001). Global improvement was reported in 14 subjects (58%) for both depression and ADHD and in 7 subjects (29%) for depression only. Common side effects were headache, nausea, rash, and irritability.

Mirtazapine

There have been two double-blind, placebo-controlled multicenter trials of mirtazapine in the treatment of child and adolescent outpatients with MDD. In these studies, mirtazapine was not superior to placebo on the primary efficacy measure of change from baseline to endpoint in CDRS-R scores (U.S. Food and Drug Administration 2004b).

Duloxetine

There have been two failed 10-week trials of duloxetine (fixed dosing, 30 mg/day and 60 mg/day; and flexible dosing, 60-120 mg/day) in the treatment of children and adolescents with MDD (Atkinson *et al.* 2014; Emslie *et al.* 2014). Duloxetine and fluoxetine were not superior to placebo on the primary efficacy measure of change from baseline to endpoint in CDRS-R scores. The most common adverse events with duloxetine were nausea, vomiting, nasopharyngitis, upper abdominal pain, headache, and somnolence.

Desvenlafaxine

The efficacy of desvenlafaxine at a low exposure (20-35 mg/day based on weight) and a higher exposure (25-50 mg/day based on weight) for the treatment of MDD in children and adolescents (ages 7-17 years) was assessed in a double-blind, placebo-controlled 8-week trial. Desvenlafaxine was not superior to placebo on the primary efficacy measure of change from baseline to week 8 in the CDRS-R total score (Atkinson *et al.* 2018). In a fluoxetine-referenced study that included 339 children and adolescents ages 7-17 years, neither desvenlafaxine (25-50 mg/day) nor fluoxetine (20 mg/day) statistically separated from placebo on the primary outcome measure of change from baseline to week 8 in CDRS-R total score (Weihs *et al.* 2018). The most common adverse events with desvenlafaxine were headache, abdominal pain, nausea, and dizziness.

Selegiline Transdermal System

In a placebo-controlled trial of 308 adolescents with MDD, selegiline transdermal system was not superior to placebo on the primary efficacy measure of change from baseline to endpoint in CDRS-R scores (DelBello *et al.* 2014). The most common adverse events for selegiline were application site reactions, headaches, and nausea.

Vilazodone

There have been two double-blind, placebo-controlled 8-week trials of vilazodone for treatment of MDD in youth (Durgam *et al.* 2018). In one trial, 529 adolescents (ages 12-17 years) were randomly assigned to vilazodone (15 mg/day), vilazodone (30 mg/day), or placebo (Durgam *et al.* 2018). There was no statistically significant difference between vilazodone (15 mg/day), vilazodone (30 mg/day), and placebo on the primary efficacy measure of change from baseline to week 8 in CDRS-R total score.

In another trial, 473 children and adolescents (ages 7-17 years) were randomly assigned to vilazodone (15 or 30 mg/day), placebo, or fluoxetine (20 mg/day) (Findling *et al.* 2020). In this failed trial, neither vilazodone nor fluoxetine was significantly superior to placebo on the primary efficacy measure of change from baseline to week 8 in the CDRS-R total score. The most common adverse events with vilazodone were nausea, headache, vomiting, diarrhea, abdominal pain, somnolence, and dizziness.

Vortioxetine

In a 6-month open-label trial, 41 youths with depressive or anxiety disorders received vortioxetine (5-20 mg/day), which showed a trend toward effectiveness (Findling *et al.* 2018).

Meta-Analysis: Pharmacological and Psychotherapeutic Treatments

A systematic review and network meta-analysis of the comparative efficacy of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depression included placebo-controlled and head-to-head comparison trials of 16 antidepressants, 7 psychotherapies, and 5 combinations of antidepressants and psychotherapy (Zhou *et al.* 2020). The quality of evidence was rated as low to very low. Only fluoxetine (alone or in combination with CBT) was more effective than both placebo and psychological control conditions.

Suicidality and Black Box Warning

In a combined analysis of 24 short-term placebo-controlled trials of antidepressant medications in child and adolescent MDD, OCD, or other psychiatric disorders, the rates of suicidality (suicidal thinking and behavior) were 4% for patients given medication and 2% for patients given placebo. There were no completed suicides in any of the clinical trials. The FDA directed manufacturers to add a black box warning to the health professional label of antidepressant medications to describe the increased risk of suicidal thoughts and behavior for children and adolescents being treated with antidepressant medications and to emphasize the need for close monitoring of patients taking the medications (U.S. Food and Drug Administration 2004a). Parents and patients should be advised of the black box warning for antidepressant medication.

In a subsequent meta-analysis of 27 trials of antidepressants in pediatric MDD, the rates of suicidal ideation and attempts were 3% in the youths treated with antidepressants and 2% in the youths who received placebo (Bridge *et al.* 2007). The investigators reported that the number needed to treat was 10, whereas the number needed to harm was 112, and therefore the benefits of antidepressants outweigh the potential risk from suicidal ideation or attempt. A number of studies, in both the United States and Europe, have failed to demonstrate an association between antidepressant use and youth suicide (Gibbons *et al.* 2006; Markowitz and Cuellar 2007;

Simon *et al.* 2006; Sondergard *et al.* 2006). It is noteworthy that the suicide rate in youths increased after the addition of the black box warning on antidepressants (Hamilton *et al.* 2007; Lu *et al.* 2020). The FDA advisory has been associated with significant decreases in the rates of diagnosis and treatment of pediatric depression (Libby *et al.* 2007; Lu *et al.* 2020). The risk of deliberate self-harm was found to be higher in youths whose treatment was initiated with high-dosage SSRIs than in those whose treatment began with SSRIs at modal dosages (i.e., usual or most common dosage) (Miller *et al.* 2014).

Treatment-Resistant Depression

In the National Institute of Mental Health (NIMH)-funded multisite Treatment of SSRI-Resistant Depression in Adolescents trial (Brent *et al.* 2008), 334 adolescents with SSRI-resistant depression were randomly assigned to one of four treatments for 12 weeks: switch to an alternative SSRI (paroxetine, citalopram, or fluoxetine), switch to an alternative SSRI plus CBT, switch to venlafaxine, or switch to venlafaxine plus CBT. CBT plus a medication switch (to venlafaxine or to an alternative SSRI) produced the highest rate of response (54.8%). Response rates (CGI-I score [?] 2 and CDRS-R [?] 50% reduction) were similar for switching to an alternative SSRI and switching to venlafaxine (47% and 48.2%, respectively). Skin problems and increases in diastolic blood pressure and pulse were more frequently experienced during venlafaxine treatment than during SSRI treatment.

To date, there have been no randomized controlled trials (RCTs) that investigated medication augmentation strategies for children and adolescents who do not respond to initial antidepressant medication.

There have been preliminary investigations of intravenous ketamine for treatment-resistant depression in adolescents. In an open-label study, 13 adolescents (ages 12-18 years) with treatment-resistant depression were administered 6 ketamine (0.5 mg/kg) infusions over 2 weeks. Response ([?] 50% decrease in CDRS-R) rate was 38%. Two of the five responders relapsed within 2 weeks, and the others showed sustained remission at 6 weeks (Cullen *et al.* 2018). In a randomized double-blind, single-dose crossover study, 17 adolescents (ages 13-17 years) with treatment-resistant depression were given a single infusion of ketamine (0.5 mg/kg over 40 minutes) or midazolam (0.045 mg/kg over 40 minutes) (Dwyer *et al.* 2021). Compared with midazolam, a single ketamine infusion produced a significantly greater reduction in depressive symptoms 24 hours after infusion based on improvement in the MADRS score. The most common adverse event with ketamine infusion was transient dissociative symptoms.

Clinical Recommendations for Major Depressive Disorder

SSRIs are first-line medication treatments for MDD in children and adolescents (American Academy of Child and Adolescent Psychiatry and American Psychiatric Association 2018).

An evidence-based consensus medication algorithm for the treatment of childhood MDD is available (Texas Children's Medication Algorithm Project [Hughes *et al.* 2007]). Based on research evidence and panel discussion, four stages of medication treatment are identified:

- Stage 1: SSRI
- Stage 2: Alternative SSRI
- Stage 2A (if partial response to SSRI): SSRI + lithium, bupropion, or mirtazapine
- Stage 3: Different class of antidepressant medication (venlafaxine, bupropion, mirtazapine, duloxetine) (Note: Since publication of this algorithm, there have been controlled trials of desvenlafaxine and vilazodone for children and adolescents with MDD.)
- Stage 4: Reassessment, treatment guidance

An additional recommendation is that antidepressants should be continued for 6-12 months after symptom remission. At the time of discontinuation of an antidepressant, the dosage should be tapered slowly (i.e., no more than 25% per week). The typical tapering and discontinuation period is 2-3 months.

Bipolar Disorder

The prevalence of bipolar disorder in a community sample of adolescents was found to be 1% (Merikangas *et al.* 2010). Although DSM-5 criteria are used to diagnose bipolar disorder in youths, children with bipolar disorder often exhibit mixed mania and rapid cycling (Geller *et al.* 2000). One-year recovery rates of 87% and relapse rates of 61%-80% have been reported in children and adolescents with bipolar disorder (Birmaher *et al.* 2020; B. Geller *et al.* 2004).

Six medications have FDA approval for the acute treatment of bipolar I disorder, mixed or manic episode, in youths: lithium (age [?] 7 years), aripiprazole (age [?] 10 years), asenapine (age [?] 10 years), olanzapine (age [?] 13 years), risperidone (age [?] 10 years), and quetiapine (age [?] 10 years). Ziprasidone has been studied for the treatment of bipolar disorder in youths, but it does not have FDA approval for that indication. Lithium also has FDA approval for use in the maintenance treatment of bipolar I disorder, mixed and manic episodes, in youths age 7 years or older.

Lithium

The efficacy of lithium for the treatment of bipolar I disorder, manic or mixed episode, was assessed in an 8-week double-blind, placebo-controlled trial involving 81 youths (ages 7-17 years) (Findling *et al.* 2015d). The mean lithium serum level at endpoint was 0.98 mEq/L. Lithium was superior to placebo on the primary outcome measure of change in Young Mania Rating Scale (YMRS) score from baseline to endpoint. On CGI-I scores, 47% of lithium-treated and 21% of placebo-treated patients were much or very much improved. The most common adverse events with lithium were vomiting, nausea, and headache. There was a statistically significant increase in thyrotropin concentration with lithium. Information on the dosing and monitoring of lithium and a discussion of side effects can be found in the appendix to this chapter.

In an NIMH-funded study, 153 children and adolescents with bipolar I disorder, mixed or manic episode, were randomly assigned to treatment with lithium, divalproex, or placebo in an 8-week trial (Kowatch *et al.* 2007). Target lithium serum levels were 0.8-1.2 mEq/L. Lithium was not significantly superior to placebo.

In a small double-blind, placebo-controlled study of lithium treatment for adolescent bipolar disorder and DSM-III-R (American Psychiatric Association 1987)-defined substance dependence (Geller *et al.* 1998), 25 adolescent outpatients were randomly assigned to either lithium (mean serum level = 0.97 mEq/L) or placebo for a 6-week trial. There was significantly greater improvement in global functioning with lithium than with placebo. Side effects in the group treated with lithium were polyuria, thirst, nausea, vomiting, and dizziness.

Atypical Antipsychotics

Information about dosages, monitoring, and adverse effects of atypical antipsychotics is provided in the appendix to this chapter.

Aripiprazole

The efficacy of aripiprazole was assessed in a 4-week double-blind, placebo-controlled trial that included 296 youths (ages 10-17 years) with bipolar I disorder, mixed or manic episode (Findling *et al.* 2009). Both low-dosage aripiprazole (10 mg/day) and high-dosage aripiprazole (30 mg/day) were significantly superior to placebo in reduction of YMRS scores. The response rate ([?] 50% reduction in YMRS score) was 44.8% for low-dosage aripiprazole, 63.6% for high-dosage aripiprazole, and 26.1% for placebo. The most common adverse events with aripiprazole were somnolence, extrapyramidal side effects (EPS), and tremor, which were more common in the high-dosage aripiprazole group. In a 26-week placebo-controlled extension phase, both aripiprazole 10 mg and 30 mg were significantly superior to placebo (Findling *et al.* 2013c).

Asenapine

The efficacy of asenapine was evaluated in a 3-week double-blind, placebo-controlled trial of 403 youths (ages 10-17 years) with bipolar I disorder, mixed or manic episode (Findling *et al.* 2015b). Dosages ranged from 2.5 to 10 mg twice daily. Asenapine was significantly superior to placebo on the outcome measure of change in YMRS from baseline to endpoint. The most comment adverse events were somnolence, dizziness, oral hypoesthesia, headache, fatigue, and increased appetite.

Olanzapine

There is one reported double-blind, placebo-controlled multicenter study of olanzapine (2.5-20 mg/day) in the treatment of adolescent outpatients with bipolar I disorder, mixed or manic episode (Tohen *et al.* 2007). Adolescents were randomly assigned to receive olanzapine ($n = 107$) or placebo ($n = 54$) for 3 weeks. Response rates (defined as [?] 50% decrease in YMRS score) were significantly greater for the olanzapine group (44.8%) than for the placebo group (18.5%). Remission rates (defined as YMRS score < 12) were also significantly greater for the olanzapine group (35.2%) than for the placebo group (11.1%). Adverse effects in the olanzapine group were hyperprolactinemia, weight gain (mean = 3.7 kg), somnolence, and sedation.

Risperidone

In a 3-week double-blind, placebo-controlled trial, the efficacy of risperidone was assessed in 169 children and adolescents (ages 10-17 years) with bipolar I disorder, manic or mixed episode (Haas *et al.* 2009a). Both low-dosage risperidone (0.5-2.5 mg/day) and high-dosage risperidone (3-6 mg/day) were significantly superior to placebo in reduction of YMRS scores. The response rate ([?] 50% reduction in baseline YMRS score) was 59% for low-dosage risperidone and 63% for high-dosage risperidone, compared with a placebo response rate of 26%. The most common adverse events with risperidone were somnolence, headache, and fatigue. EPS were more common in the high-dosage risperidone group than in the low-dosage group.

Quetiapine

In a 3-week double-blind, placebo-controlled trial, the efficacy of quetiapine was assessed in 277 youths (ages 10-17 years) with bipolar I disorder, manic or mixed episode (Pathak *et al.* 2013). Both low-dosage quetiapine (400 mg/day) and high-dosage quetiapine (600 mg/day) were significantly superior to placebo in reduction of YMRS scores. The response rate ([?] 50% reduction in baseline YMRS score) was 55% for low-dosage quetiapine, 56% for high-dosage quetiapine, and 28% for placebo. The most common adverse events with quetiapine were somnolence, sedation, dizziness, and headache.

Ziprasidone

The efficacy of ziprasidone was assessed in a 4-week double-blind, placebo-controlled trial that included 237 youths (ages 10-17 years) with bipolar I disorder, manic or mixed episode (Findling *et al.* 2013b). Ziprasidone dosages ranged from 40 to 160 mg/day. Ziprasidone was significantly superior to placebo in reduction of YMRS scores. A [?] 50% reduction in YMRS scores was achieved by 53% of the ziprasidone-treated group and 22% of the placebo group. The most common side effects with ziprasidone were sedation, somnolence, headache, fatigue, and nausea.

Mood Stabilizers

Information about dosages, monitoring, and adverse effects of mood stabilizers is provided in the appendix to this chapter.

Divalproex

A 4-week double-blind, placebo-controlled multicenter trial of 150 youths (ages 10-17 years) with bipolar I disorder, mixed or manic episode, did not show a significant difference in reduction in YMRS scores from baseline to endpoint between patients given divalproex extended release (ER) and those given placebo (Wagner *et al.* 2009). The mean modal dose of divalproex ER was 1,286 mg. There were no statistically significant differences in adverse-event incidence between the divalproex ER and placebo groups. Gastrointestinal symptoms were more commonly reported with divalproex ER than with placebo.

Carbamazepine

In an open-label study of carbamazepine ER in 137 youths (ages 10-17 years) with bipolar I disorder, mixed or manic episode, there was a statistically significant reduction in scores on the YMRS from baseline to endpoint (Findling and Ginsberg 2014). At endpoint, the most prevalent dosage of carbamazepine ER was 1,200 mg/day. The most common adverse events were rash, decreased white blood cell count, nausea, and vomiting.

Oxcarbazepine

In a double-blind, placebo-controlled multicenter trial of oxcarbazepine for the treatment of children and adolescents (ages 7-12 years) with bipolar I disorder, mixed or manic episode, 116 youths received oxcarbazepine (mean dosage = 1,515 mg/day) or placebo for a 7-week trial (Wagner *et al.* 2006b). There was no significant difference in reduction in YMRS scores at endpoint between the oxcarbazepine and placebo groups. The most common side effects in the oxcarbazepine-treated patients were dizziness, nausea, somnolence, diplopia, fatigue, and rash.

Topiramate

A double-blind, randomized, placebo-controlled multicenter study assessing the efficacy of topiramate treatment in children and adolescents with acute mania was designed as a 200-patient study but was terminated after random assignment of 56 patients (ages 6-17 years) when adult mania trials did not show efficacy (DelBello *et al.* 2005). Dosages were titrated to 400 mg/day (mean dosage = 278 mg/day). Over a 4-week period, no significant difference was found between the topiramate and placebo groups. The most common adverse events in the topiramate group included decreased appetite, nausea, diarrhea, paresthesias, and somnolence.

Lamotrigine

In a 12-week open-label trial, the efficacy of lamotrigine was assessed in 30 children and adolescents with bipolar spectrum disorders (Biederman *et al.* 2010). The mean lamotrigine dosage at endpoint was 160.7 mg/day. Significant improvement in mean YMRS scores was reported; however, only about half the participants completed the trial, and seven participants discontinued lamotrigine because of rash.

Comparator Studies

The Treatment of Early Age Mania study compared the effectiveness of risperidone, lithium, and divalproex in the treatment of 279 youths (ages 6-15 years) with bipolar I disorder, manic or mixed episode (Geller *et al.* 2012). Response was defined as a CGI-Bipolar Disorder-Improvement Mania score of 2 or lower. The mean lithium serum level was 1.09 mEq/L, the mean divalproex level was 113.6 mg/mL, and the mean risperidone dosage was 2.57 mg/day. The risperidone response rate (68.5%) was significantly higher than response rates for lithium (35.6%) and divalproex (24%). There was no significant difference between lithium and divalproex response rates. Increased weight gain, BMI, and prolactin levels were significantly more common with risperidone than with lithium or divalproex. There were also higher response rates for nonresponders who switched to risperidone and partial responders augmented with risperidone than for lithium and divalproex (Walkup *et al.* 2015).

Similarly, a comparator analysis of the efficacy of antipsychotics and mood stabilizers for the treatment of pediatric bipolar disorder showed significantly greater improvement in YMRS scores for patients given antipsychotics than for those given mood stabilizers (Correll *et al.* 2010). Effect sizes were 0.65 for antipsychotics and 0.24 for mood stabilizers.

The comparative efficacy of lithium, divalproex, and carbamazepine was assessed in a 6-week randomized open-label trial involving 42 children and adolescents with bipolar disorder (Kowatch *et al.* 2000b). There were no significant differences in response rates ([?] 50% reduction in YMRS score) among the groups given lithium (38%), divalproex (53%), and carbamazepine (38%).

The comparative efficacy of risperidone and divalproex was assessed in an 8-week double-blind, randomized trial of 66 children and adolescents with bipolar disorder (Pavuluri *et al.* 2010). A significantly higher response rate ([?] 50% reduction in YMRS) was found for risperidone (78.1%) than for divalproex (45.5%), and improvement was more rapid in risperidone-treated patients than in divalproex-treated patients.

The comparative efficacy of quetiapine and divalproex was assessed in a 4-week double-blind, placebo-controlled trial involving 50 adolescents with bipolar I disorder, manic or mixed episode (DelBello *et al.* 2006). No significant group differences were found in reduction in YMRS scores during the trial.

In an 8-week open-label trial, the efficacies of olanzapine and risperidone were compared in preschool-age children with bipolar disorder (Biederman *et al.* 2005). There were no significant differences in response rates between risperidone (69%) and olanzapine (53%).

In a 6-week placebo-controlled trial of valproic acid versus risperidone for children (ages 3-7 years) with bipolar disorder, manic, mixed, or hypomanic episode, risperidone was superior to placebo on reduction in YMRS scores from baseline to endpoint. No significant difference was found between valproic acid and placebo (Kowatch *et al.* 2015).

Combination Treatment

Some children with bipolar disorder may not respond to initial monotherapy treatment or may need combination treatment over the course of the illness. For example, in a study by Kowatch *et al.* (2000a), after acute 6-week treatment with one mood stabilizer, 20 of 35 youths (58%) needed additional psychotropic medication over the next 16 weeks. The response rate to combination treatment with two mood stabilizers was high (80%) for youths who did not respond to monotherapy.

The FDA has approved the use of quetiapine or aripiprazole as an adjunct to lithium or valproate treatment in children ages 10 years and older with bipolar I disorder, mixed or manic episode.

The effectiveness of combination treatment with lithium and divalproex was assessed in an open trial (Findling *et al.* 2003). Ninety youths (ages 5-17 years) with bipolar I or II disorder were treated for up to 20 weeks with divalproex (mean blood level = 79.8 mg/mL) and lithium (mean blood level = 0.9 mmol/L). The clinical remission rate (defined as contiguous weekly ratings of YMRS scores [?] 12.5, CDRS-R scores [?] 40, Children's Global Assessment Scale scores [?] 51, clinical stability, and no mood cycling) was 42%.

The efficacy of risperidone in combination with lithium or divalproex was assessed in a 6-month open-label trial (Pavuluri *et al.* 2004). Thirty-seven youths (ages 5-18 years) with bipolar I disorder, manic or mixed episode, received either risperidone (mean dosage = 0.75 mg/day) plus divalproex (mean serum level = 106 mg/mL) or risperidone (mean dosage = 0.70 mg/day) plus lithium (mean serum level = 0.9 mEq/L). Response rates ([?] 50% reduction in baseline YMRS scores) were similar for both combinations: 80% for divalproex plus risperidone and 82.4% for lithium plus risperidone. There were no significant differences between the groups in safety and tolerability.

Risperidone augmentation for lithium nonresponders was assessed in a 1-year open-label study (Pavuluri *et al.* 2006). Twenty-one of 38 youths (ages 4-17 years) who did not respond to lithium monotherapy or relapsed after initial response were given risperidone (mean dosage = 0.99 mg/day) for 11 months. The response rate in the lithium plus risperidone group was 85.7%.

In a double-blind, placebo-controlled study of quetiapine, 30 adolescents with bipolar disorder received divalproex (20 mg/kg) and were randomly assigned to adjunctive quetiapine (mean daily dosage = 432 mg) or placebo for 6 weeks (DelBello *et al.* 2002). The response rate ([?] 50% reduction in baseline YMRS score) was significantly higher in the group receiving divalproex and quetiapine (87%) than in the group receiving divalproex and placebo (53%).

No significant differences were found between lithium plus risperidone and lithium plus quetiapine in reduction in YMRS scores for 30 youths hospitalized for a manic or mixed episode (Habibi *et al.* 2017).

Celecoxib adjunctive to lithium and risperidone was assessed in an 8-week double-blind, placebo-controlled trial in 42 adolescents with bipolar I disorder, manic episode (Mousavi *et al.* 2017). Significantly greater improvement in YMRS scores was found for the celecoxib group than for the placebo group. The researchers suggested that the mood-stabilizing role of celecoxib might be through its action on inflammatory cascades.

Maintenance Treatment

Clinical outcomes with lithium compared with other mood stabilizer medications were evaluated in a longitudinal study of 340 youths (ages 7 years to 17 years, 11 months) with DSM-IV (American Psychiatric Association 1994)-defined bipolar disorder I, II, or not otherwise specified over a 10-year period (Hafeman *et al.* 2020). The lithium group had significantly fewer suicide attempts, fewer depressive symptoms, less psychosocial impairment, and less aggression.

Lithium in the maintenance treatment of bipolar I disorder, mixed or manic, has been assessed in a randomized, double-blind, placebo-controlled discontinuation study of youths ages 7 to 17 years (Findling *et al.* 2019). Responders to lithium treatment from one of two previous multiphase studies received up to 28 weeks of either continued lithium treatment (mean lithium dosage 1,394 mg/day at start of discontinuation trial) or placebo. Youths who continued lithium treatment (*n* = 17) had a significantly lower hazard ratio (0.28) compared with those in the placebo group (*n* = 15). Most study discontinuations were due to mood symptom exacerbations, particularly in the placebo group.

There have been two maintenance studies of aripiprazole for treatment of bipolar disorder in youths. A 72-week double-blind, placebo-controlled maintenance study of aripiprazole in children (ages 4-9 years) with bipolar I, II, or not otherwise specified showed that time to discontinuation due to a mood event was significantly longer in the aripiprazole group than the placebo group (Findling *et al.* 2012b). In a randomized double-blind 30-week placebo-controlled trial of aripiprazole for maintenance treatment in bipolar I disorder, manic or mixed, in youth ages 10-17 years, both dosages of aripiprazole (10 mg/day and 30 mg/day) showed significantly greater improvement in YMRS total score compared with placebo during the 26-week extension phase (Findling *et al.* 2013c).

Sixty youths who had responded to a combination of lithium and divalproex in a 20-week trial were randomly assigned in a double-blind trial to either lithium or divalproex for 18 months (Findling *et al.* 2005). There was no significant difference in the time to relapse between the groups (median days: divalproex 112, lithium 114).

Lamotrigine efficacy for maintenance treatment of pediatric bipolar disorder has been assessed in two trials. In a 14-week open-label trial that included 46 youths (ages 8-18 years) with mania or hypomania, lamotrigine improved depressive and manic symptoms (Pavuluri *et al.* 2009). Adjunctive maintenance lamotrigine for bipolar disorder in 10-to 17-year-olds was evaluated in a placebo-controlled randomized withdrawal study. There were no significant differences between the lamotrigine group and the placebo group in the time to occurrence of a bipolar event (Findling *et al.* 2015a).

Bipolar Depression

Two medications have FDA approval for bipolar I disorder, major depressive episode: lurasidone (age [?] 10 years) and olanzapine/fluoxetine combination (age [?] 10 years).

Lurasidone

The efficacy of lurasidone for 347 children and adolescents ages 10-17 years with bipolar I disorder, major depressive episode, was assessed in a double-blind, placebo-controlled 6-week trial (DelBello *et al.* 2017). Lurasidone dosage range was 20-80 mg/day. There was a statistically significantly greater improvement in CDRS-R total score for the lurasidone group compared with the placebo group. The most common adverse events with lurasidone were nausea and somnolence.

A post hoc analysis of this trial showed that lurasidone was efficacious for youths with bipolar depression with mixed (subsyndromal hypomania) features (Singh *et al.* 2020).

Olanzapine/Fluoxetine Combination

Two hundred twenty-five youths (ages 10-17 years) with bipolar I disorder, major depressive episode, were randomly assigned to olanzapine/fluoxetine combination (OFC; dosage range 3 mg olanzapine/25 mg fluoxetine to 12/50 mg/day) or placebo in an 8-week double-blind randomized trial (Detke *et al.* 2015). OFC-treated patients had significantly greater changes in CDRS total score from baseline to week 8. The most common adverse events with OFC were weight gain, increased appetite, and somnolence, as well as hyperlipidemia.

Quetiapine

Quetiapine XR was not significantly superior to placebo in an 8-week double-blind, placebo-controlled trial of 193 youths (ages 10-17 years) with bipolar I disorder, major depressive episode (Findling *et al.* 2014). Similarly, a double-blind, placebo-controlled pilot study of treatment of adolescents with bipolar I disorder, major depressive episode, did not show statistically significant differences between quetiapine and placebo from baseline to endpoint on CDRS-R total scores (DelBello *et al.* 2009).

Lithium

To date, there are no controlled studies of lithium for the treatment of bipolar I disorder, major depressive episode, in youths. An open-label study showed improvement in depressive symptoms (Patel *et al.* 2006).

Lamotrigine

To date, there are no controlled studies of lamotrigine for the treatment of bipolar I disorder, major depressive episode, in youths. Open-label studies have shown some effectiveness, with improvement in depressive symptoms (Biederman *et al.* 2010; Chang *et al.* 2006).

Clinical Recommendations for Bipolar Disorder

Treatment guidelines were developed by expert consensus and review of the available treatment literature for children and adolescents (ages 6-17 years) with bipolar I disorder, manic or mixed episode (Kowatch *et al.* 2005). Six stages were identified:

- Stage 1: Monotherapy with mood stabilizer or atypical antipsychotic
- Stage 2: Switch monotherapy agent (drug class not tried in stage 1)
- Stage 3: Switch monotherapy agent (drug class not tried in stage 1 or 2) OR combination treatment (two agents)
- Stage 4: Combination treatment (with two agents) OR combination treatment (with three agents)
- Stage 5: Alternative monotherapy (drugs not tried in stages 1, 2, or 3)
- Stage 6: Electroconvulsive therapy (adolescents) or clozapine

If a child does not respond to treatment in one stage, the clinician should move to the next stage of treatment. For treatment of bipolar I disorder, manic or mixed episode

with psychosis, the recommendation for initial treatment is a mood stabilizer plus an atypical antipsychotic. A minimum of 4 weeks at therapeutic blood levels or adequate dosages for each medication is recommended. After sustained remission of at least 12 months, medication taper should be considered.

Anxiety Disorders

DSM-5 anxiety disorders include generalized anxiety disorder, social anxiety disorder, panic disorder, selective mutism, agoraphobia, specific phobia, and separation anxiety disorder. OCD and PTSD are now in separate DSM-5 categories (Obsessive-Compulsive and Related Disorders and Trauma-and Stressor-Related Disorders, respectively).

Generalized Anxiety Disorder

The lifetime prevalence of generalized anxiety disorder (GAD) in adolescents is reported to be 2.2% (Merikangas *et al.* 2010). Children with GAD have excessive anxiety and worry about several events or activities (e.g., school performance), have difficulty controlling the worry, and have at least one associated symptom, such as restlessness, fatigue, concentration difficulties, irritability, muscle tension, or sleep disturbance (American Psychiatric Association 2013). The course of GAD in youths tends to be persistent (Kessler *et al.* 2012).

Duloxetine

Duloxetine has been approved by the FDA for the treatment of GAD in youths ages 7-17 years. The efficacy of duloxetine was assessed in a 10-week double-blind, placebo-controlled trial for 272 youths (ages 7-17 years) with GAD (Strawn *et al.* 2015a). Duloxetine was flexibly dosed from 30 to 120 mg/day. The primary efficacy measure was the Pediatric Anxiety Rating Scale (PARS). Duloxetine was significantly superior to placebo on improvement in PARS scores from baseline to endpoint. Response (defined as 50% improvement in PARS severity for GAD) and remission (defined as PARS severity score for GAD [?] 8) were significantly greater for the duloxetine group (59% and 50%, respectively) than the placebo group (42% and 34%, respectively). Adverse events reported with significantly greater frequency for the duloxetine group than for the placebo group were nausea, vomiting, decreased appetite, oropharyngeal pain, dizziness, cough, and palpitations.

Venlafaxine

The efficacy of venlafaxine XR for children and adolescents with GAD ($N = 320$) was evaluated in two double-blind, placebo-controlled trials (Rynn *et al.* 2007). Venlafaxine was given at dosages up to 225 mg/day. In one study, venlafaxine XR was superior to placebo on primary and secondary measures; however, in the other study, the results were negative.

Sertraline

Twenty-two children and adolescents (ages 5-17 years) with GAD were randomly assigned to sertraline or placebo in a 9-week double-blind trial (Rynn *et al.* 2001). The maximum dosage of sertraline was 50 mg/day. Significant differences in favor of sertraline over placebo were observed on the Hamilton Anxiety Scale scores and on CGI Severity of Illness (CGI-S) and CGI-I ratings. Side effects found to be more common (but not statistically significantly so) with sertraline than with placebo were dry mouth, drowsiness, leg spasm, and restlessness.

Escitalopram

The efficacy of escitalopram for the treatment of GAD in 51 adolescents (ages 12-17 years) was investigated in a double-blind, placebo-controlled 8-week trial (Strawn *et al.* 2020). Escitalopram dosages ranged from 15 mg/day to 20 mg/day. Escitalopram was significantly superior to placebo in reduction of anxiety symptoms.

Buspirone

There have been two unpublished randomized placebo-controlled trials of buspirone in young patients (ages 6-17 years) with GAD (U.S. Food and Drug Administration 1998, 2000). A Bayesian approach for the reanalysis of the summary data was performed (Strawn *et al.* 2018a). In the flexibly dosed ($N = 227$) and fixed-dose ($N = 341$) trials, buspirone did not separate from placebo on the outcome measure of improvement in the sum of the Columbia Schedule for Affective Disorders and Schizophrenia GAD items. Dosages ranged from 15 mg/day to 60 mg/day. Light-headedness occurred more frequently in the buspirone group than in the placebo group.

Social Anxiety Disorder

The prevalence of social anxiety disorder in adolescents is reported to be 9.1% (Merikangas *et al.* 2010). The DSM-5 diagnostic criteria for social anxiety disorder are the same for children and adolescents as for adults.

Social anxiety disorder in youth is a chronic condition, and it increases the risk of depression (Stein *et al.* 2001).

Selective Serotonin Reuptake Inhibitors

Paroxetine. The efficacy and safety of paroxetine were evaluated in a 16-week double-blind, placebo-controlled multicenter trial of 322 outpatient children and adolescents (ages 8-17 years) with social anxiety disorder (Wagner *et al.* 2004a). Paroxetine was significantly superior to placebo, with rates of response (defined as CGI-I score = 1 or 2) of 77.6% and 38.3%, respectively. Side effects more common with paroxetine than with placebo were insomnia, decreased appetite, and vomiting.

Fluoxetine. The efficacy of fluoxetine was evaluated in a 12-week randomized trial of fluoxetine (up to 40 mg/day), psychotherapy (Social Effectiveness Therapy for Children), or placebo in 80 youths (ages 7-17 years) with social anxiety disorder (Beidel *et al.* 2007). Both fluoxetine and Social Effectiveness Therapy for Children were superior to placebo in reducing social stress and behavioral avoidance and increasing general functioning.

Sertraline. Fourteen outpatient children and adolescents (ages 10-17 years) with a diagnosis of social anxiety disorder received sertraline (dosage range = 100-200 mg/day; mean daily dosage = 123 mg) in an 8-week open trial (Compton *et al.* 2001). Five of the patients (36%) were much or very much improved, and four of the patients (29%) had a partial response by the end of the 8-week trial. Sertraline was well tolerated, and no patient developed significant behavioral disinhibition or mania (Compton *et al.* 2001).

Escitalopram. Twenty children with social anxiety disorder participated in a 12-week open-label study of escitalopram (Isolan *et al.* 2007). Sixty-five percent of participants were much or very much improved.

Citalopram. Chavira and Stein (2002) investigated the effectiveness of a combined psychoeducational and pharmacological treatment program for youths with social anxiety disorder. Twelve children and adolescents (ages

8-17 years) with social anxiety disorder received citalopram (mean daily dosage = 35 mg) and eight 15-minute counseling sessions over a 12-week period. On the basis of clinical global ratings of change, five of the patients (41.7%) were very much improved, and five of the patients (41.7%) were much improved.

Venlafaxine

In a 16-week double-blind, placebo-controlled trial, 293 children and adolescents with social anxiety disorder were randomly assigned to venlafaxine XR (dosage range = 37.5-225 mg/day) or placebo (March *et al.* 2007). Venlafaxine XR was significantly superior to placebo in reducing ratings of social anxiety. Response rates (CGI-I score [?] 2) were 56% for the venlafaxine XR group and 37% for the placebo group.

Panic Disorder

The lifetime prevalence of panic disorder in adolescents is reported to be 2.3%. The DSM-5 diagnostic criteria for panic disorder in children and adolescents are the same as those for adults. Panic disorder in youths is a chronic condition, and there is continuity between pediatric and adult panic disorder (Biederman *et al.* 1997).

Selective Serotonin Reuptake Inhibitors

In an open-label trial, 12 children and adolescents (ages 7-17 years) with panic disorder were treated with an SSRI for 6-8 weeks (Renaud *et al.* 1999). Mean daily dosages of SSRIs were fluoxetine 34 mg, paroxetine 20 mg, and sertraline 125 mg. Adjunctive benzodiazepines were used for 8 patients. Seventy-five percent of patients showed much to very much clinical improvement while receiving treatment with SSRIs. At the end of the trial, 8 patients (67%) no longer fulfilled panic disorder criteria.

Paroxetine. A chart review was conducted of 18 child and adolescent outpatients (ages 7-16 years) with a diagnosis of panic disorder who received monotherapy with paroxetine (dosage range = 10-40 mg/day; mean daily dosage = 23 mg) (Masi *et al.* 2001). The mean paroxetine treatment duration was 11.7 months. Fifteen patients (83%) had a CGI-I score of much or very much improved. The most common side effects were nausea, tension, agitation, sedation, insomnia, palpitations, and headache.

Citalopram. Three youths (ages 9, 13, and 16 years) with panic disorder and school phobia were treated with citalopram (up to 20 mg/day) over an 8-to 15-month period. All patients experienced resolution of panic attacks during the course of citalopram treatment (Lepola *et al.* 1996).

Benzodiazepines

In a 2-week open trial, four adolescents with panic disorder were treated with clonazepam (0.5 mg twice daily). A significant reduction in panic attacks (from 3 attacks per week to 0.25 per week) was reported (Kutcher and MacKenzie 1988).

Mixed Anxiety Disorders

Selective Serotonin Reuptake Inhibitors

Fluvoxamine. One hundred twenty-eight outpatient children and adolescents (ages 6-17 years) with GAD, social anxiety disorder, or separation anxiety disorder (who had received 3 weeks of open treatment with supportive psychoeducational therapy without improvement) were randomly assigned to fluvoxamine (up to 300 mg/day) or placebo for an 8-week trial (Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001). The group treated with fluvoxamine had a significantly greater reduction in PARS scores than did the placebo group. The response rate (CGI-I score [?] 3) was 76% in the group being treated with fluvoxamine and 29% in the group receiving placebo. After completion of the 8-week placebo-controlled study, the 128 patients entered a 6-month open-label treatment phase in which fluvoxamine responders continued on fluvoxamine, fluvoxamine nonresponders were switched to fluoxetine, and placebo nonresponders were switched to fluvoxamine (Walkup *et al.* 2002). Anxiety symptoms remained low in 33 of the 35 subjects (94%) who initially responded to fluvoxamine. Of 14 fluvoxamine nonresponders switched to fluoxetine, anxiety symptoms significantly improved in 10 patients (71%). Among 48 placebo nonresponders, 27 (56%) showed significant improvement in anxiety on fluvoxamine.

Fluoxetine. Seventy-four youths (ages 7-17 years) with GAD, separation anxiety disorder, or DSM-IV-defined social phobia (i.e., DSM-5 social anxiety disorder) were randomly assigned to fluoxetine (20 mg/day) or placebo for 12 weeks (Birmaher *et al.* 2003). Sixty-one percent of fluoxetine-treated patients and 35% of placebo-treated patients were much or very much improved.

Fluoxetine's efficacy in long-term treatment of children with GAD, separation anxiety disorder, and DSM-IV social phobia was assessed in a 1-year open treatment (Clark *et al.* 2005) following the acute-phase study described above (Birmaher *et al.* 2003). Compared with youths taking no medication, those taking fluoxetine (*n* = 42) showed significantly superior outcomes on anxiety measures.

The comparative efficacy of fluoxetine and clomipramine was evaluated in a 12-week double-blind, randomized, placebo-controlled trial for 36 youths (ages 7-17 years) with GAD, separation anxiety, or social anxiety disorder (da Costa *et al.* 2013). Although all groups showed significant improvement, no significant difference was found between fluoxetine and placebo or between clomipramine and placebo.

Sertraline. The comparative efficacy of sertraline, CBT, sertraline plus CBT, and placebo was evaluated in a 12-week RCT (the Child Anxiety Multimodal Study) involving 488 children and adolescents with a diagnosis of GAD, separation anxiety disorder, or DSM-IV social phobia (Walkup *et al.* 2008). Combination treatment was significantly superior to sertraline alone and CBT alone. Rates of response (CGI-I score [?] 2) were 80.7% for combined treatment, 59.7% for CBT, and 54.9% for sertraline. All treatments were significantly superior to placebo (23.7%).

Long-term outcomes from the Child Anxiety Multimodal Study have been reported (Piacentini *et al.* 2014). At 24 and 36 weeks, most ([?] 80%) of the acute responders maintained a positive response. Combination treatment maintained an advantage over CBT alone and sertraline alone. A 4-to 12-year follow-up showed that about 22% of youths were in stable remission, 30% were chronically ill, and 48% relapsed (Ginsburg *et al.* 2018). Treatment type was not associated with remission status.

Guanfacine.

Extended-release guanfacine was assessed for the treatment of GAD, separation anxiety disorder, and social anxiety disorder in youths ages 6-17 years (Strawn *et al.* 2017). Youths received flexibly dosed (1-6 mg/day, *n* = 62) guanfacine extended release or placebo (*n* = 21) for 12 weeks. No differences were found between the treatment groups on PARS and Screen for Child Anxiety Related Emotional Disorders scores.

Meta-Analyses: Pharmacological and Psychotherapeutic Treatments

A systematic review and meta-analysis of RCTs of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) in youths with anxiety disorders (including 1,673 participants and six medications) demonstrated efficacy and moderate effect size (Cohen's *d* = 0.62), with effect size correlated with serotonergic specificity of the agent (Strawn *et al.* 2015b).

A meta-analysis of data from nine randomized, parallel group, placebo-controlled antidepressant trials (SSRIs, five trials; SNRIs, four trials) for pediatric anxiety disorders (GAD, separation anxiety disorders, and social anxiety disorder) showed that antidepressant-related improvement occurred early in treatment, and SSRIs had more rapid and greater improvement than SNRIs (Strawn *et al.* 2018b).

A systematic review of the effectiveness of CBT and pharmacotherapy in randomized and nonrandomized comparative studies for pediatric anxiety disorders (GAD, separation anxiety disorder, social anxiety disorder, specific phobias, and panic disorder) showed SSRIs and CBT to be most effective in reducing childhood anxiety symptoms; SNRIs also appear to be effective, but the evidence was less consistent (Wang *et al.* 2017). A network meta-analysis of double-blind, placebo-controlled trials of pharmacotherapy for pediatric anxiety disorders (GAD, social anxiety disorder, and separation anxiety disorder) found that only SSRIs were superior in reducing anxiety and in likelihood of treatment response compared with placebo (OR = 4.6) (Dobson *et al.* 2019). SNRIs and a_2-agonist treatment were associated with more frequent treatment response than placebo. The likelihood of treatment response was greater for SSRIs compared with SNRIs (OR = 1.9).

Clinical Recommendations for Anxiety Disorders

The American Academy of Child and Adolescent Psychiatry (AACAP) developed Clinical Practice Guidelines for Treatment of Children and Adolescents with Anxiety Disorders (Walter *et al.* 2020). With regard to medication, AACAP recommends that SSRIs be offered to patients ages 6-18 years with social anxiety, generalized anxiety, separation anxiety, or panic disorder. Clinically significant improvement in anxiety symptoms by week 6 and maximal improvement by week 12 or later has been shown with SSRIs (Strawn *et al.* 2018b).

AACAP suggests that SNRIs also can be offered to patients ages 6-18 years with social anxiety, generalized anxiety, separation anxiety, or panic disorder. In regard to duration of treatment with antidepressants for anxiety disorders, it is generally recommended that medications be maintained at an effective tolerated dosage for approximately 12 months after remission.

Obsessive-Compulsive Disorder

OCD has a prevalence rate of 2%-4% in youths (Douglass *et al.* 1995; Zohar 1999). The DSM-5 criteria for OCD are the same in children and adults. Pooled remission rates averaging 62% in long-term follow-ups have been reported (Liu *et al.* 2021).

Serotonin Reuptake Inhibitors

Four medications have received FDA approval for the treatment of OCD in children and adolescents: sertraline (age [?] 6 years), fluoxetine (age [?] 7

years), fluvoxamine (age [?] 7 years), and clomipramine (age [?] 10 years). Citalopram and paroxetine have been studied for treatment of OCD in youths but do not have FDA approval. Information about dosages, monitoring, and adverse effects of serotonin reuptake inhibitors is provided in the appendix to this chapter.

Sertraline

In a double-blind, placebo-controlled multicenter study, 187 children and adolescents (ages 6-17 years) with OCD were randomly assigned to sertraline or placebo (March *et al.* 1998). Sertraline dosages were titrated to a maximum of 200 mg/day during the first 4 weeks of the trial, and these dosages were maintained for an additional 8 weeks. The mean dosage of sertraline was 167 mg/day at endpoint. Compared with patients receiving placebo, patients receiving sertraline showed significantly greater improvement on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the NIMH Global Obsessive Compulsive Rating Scale, and the CGI-S and CGI-I subscales. Forty-two percent of patients in the sertraline group and 26% of patients in the placebo group were rated as very much or much improved. Side effects of insomnia, nausea, agitation, and tremor occurred significantly more often in the group receiving sertraline than in the group receiving placebo.

In an assessment of the long-term safety and effectiveness of sertraline for pediatric OCD, 137 patients who completed the 12-week double-blind, placebo-controlled sertraline study (March *et al.* 1998) were given open-label sertraline (mean dosage = 120 mg/day) in a 52-week extension study. Significant improvement was found on CY-BOCS, NIMH Global Obsessive Compulsive Rating Scale, and CGI scores. Rates of response (defined as > 25% decrease in CY-BOCS and a CGI-I score of 1 or 2) were 72% for children and 61% for adolescents (Cook *et al.* 2001). Full remission (defined as a CY-BOCS score < 8) was achieved in 47% of patients, and an additional 25% achieved partial remission (CY-BOCS score > 8 but < 15) (Wagner *et al.* 2003b). The most common side effects were headache, nausea, diarrhea, somnolence, abdominal pain, hyperkinesias, nervousness, dyspepsia, and vomiting.

The relative and combined efficacies of sertraline and CBT were assessed in a 12-week trial for 112 children and adolescents (ages 7-17 years) with OCD (Pediatric OCD Treatment Study [POTS] Team 2004). Patients were randomly assigned to sertraline, CBT, combined sertraline and CBT, or placebo. Combined treatment was significantly superior to CBT alone and sertraline alone, which did not differ from each other.

The efficacy of sequential sertraline and CBT compared with CBT and placebo was assessed in an 18-week trial for 47 youths (ages 7-17 years) with OCD (Storch *et al.* 2013). No significant difference was found between the groups on improvement in OCD symptoms.

Fluoxetine

A small double-blind crossover trial of fluoxetine and placebo in 14 children and adolescents (ages 8-15 years) with OCD was conducted (Riddle *et al.* 1992). After 8 weeks, CY-BOCS total score decreased significantly more in the fluoxetine group than in the placebo group (44% vs. 27%).

The safety and efficacy of fluoxetine were assessed in a 13-week double-blind, placebo-controlled multicenter trial (Geller *et al.* 2001). One hundred three children and adolescents (ages 7-17 years) with OCD were randomly assigned in a 2:1 ratio to either fluoxetine (dosage range = 10-60 mg/day; mean daily dosage = 24.6 mg) or placebo. The group treated with fluoxetine showed a statistically significantly greater reduction in OCD severity compared with the placebo group, as determined by changes in CY-BOCS scores. Rates of response (defined as > 40% reduction in CY-BOCS score) were 49% in the fluoxetine group and 25% in the placebo group. There were no significant differences in treatment-emergent adverse events between the fluoxetine and placebo groups.

Fluoxetine was compared with placebo in a controlled trial of 43 children and adolescents with OCD (Liebowitz *et al.* 2002). After 16 (but not 8) weeks of treatment, the fluoxetine group had significantly lower CY-BOCS scores than the placebo group.

Fluvoxamine

The safety and efficacy of fluvoxamine were evaluated in a double-blind, placebo-controlled multicenter study (Riddle *et al.* 2001). One hundred twenty outpatient children and adolescents (ages 8-17 years) with OCD were randomly assigned to receive fluvoxamine (dosage range = 50-200 mg/day; mean daily dosage = 165 mg) or placebo for a 10-week trial. Patients who did not respond after 6 weeks could discontinue the double-blind phase and enter an open-label trial of fluvoxamine. Mean scores on the CY-BOCS were significantly different for the fluvoxamine and placebo groups at weeks 1, 2, 3, 4, 6, and 10. Response rates (> 25% reduction in CY-BOCS scores) were 42% in the fluvoxamine group and 26% in the placebo group. Adverse events occurring at a placebo-adjusted frequency of greater than 10% were insomnia and asthenia.

Clomipramine

Clomipramine has been shown to be efficacious in the treatment of pediatric OCD in two double-blind, placebo-controlled trials. In the first study (Flament *et al.* 1985), 19 children (ages 10-18 years) with OCD were randomly assigned to clomipramine (dosage range = 100-200 mg/day; mean daily dosage = 141 mg) or placebo for 5 weeks. Significant improvement in observed and self-reported obsessions and compulsions was found for patients who received clomipramine. The most common side effects with clomipramine were tremor, dry mouth, dizziness, and constipation. One patient had a grand mal seizure.

In an 8-week double-blind, placebo-controlled multicenter study of 60 children and adolescents (ages 10-17 years) with OCD, it was found that patients who received clomipramine (up to 200 mg/day) had significantly greater reductions in scores on the

CY-BOCS than the placebo group (37% and 8%, respectively). Forty-seven patients continued in a 1-year open-label extension trial, and effectiveness was maintained with long-term treatment. The most common side effects with clomipramine were dry mouth, somnolence, dizziness, fatigue, tremor, headache, constipation, and anorexia (DeVeaugh-Geiss *et al.* 1992).

Citalopram

The efficacy of citalopram compared with fluoxetine was assessed for 29 children and adolescents (ages 7-18 years) with OCD in a 6-week RCT (Alaghband-Rad and Hakimshooshtary 2009). Both the citalopram and fluoxetine groups showed significant improvement from baseline on CY-BOCS, and there was no significant difference in efficacy between groups.

Twenty-three child and adolescent outpatients (ages 9-18 years) with OCD were given open-label citalopram (dosage range = 10-40 mg/day; mean daily dosage = 37 mg) in a 10-week trial (Thomsen 1997). There was a statistically significant improvement in CY-BOCS scores from baseline to endpoint. Adverse effects were minimal and transient.

In an 8-week open-label citalopram study of 15 youths (ages 6-17 years) with OCD, 14 patients showed significant improvement in CY-BOCS scores from baseline to endpoint (Mukaddes and Abali 2003).

In a long-term open study of 30 adolescents with OCD, citalopram (dosage range = 20-70 mg/day; mean daily dosage = 46.5 mg) was administered for 1-2 years (Thomsen *et al.* 2001). There was a significant reduction in CY-BOCS scores from baseline to assessment at 2 years. No serious adverse events were reported, and the most common side effects were sedation, sexual dysfunction, and weight gain.

Paroxetine

The efficacy and safety of paroxetine were assessed in a double-blind, placebo-controlled multicenter study of 203 outpatient children and adolescents (ages 7-17 years) with OCD (D. A. Geller *et al.* 2004). Patients were randomly assigned to paroxetine (dosage range = 10-50 mg/day; mean daily dosage = 23 mg) or placebo for a 10-week trial. There was a statistically significantly greater reduction in CY-BOCS scores from baseline to endpoint in patients treated with paroxetine than in patients treated with placebo. Response rates (> 25% reduction in CY-BOCS scores) were 64.9% in the paroxetine-treated patients and 41.2% in the placebo-treated patients. The most common adverse effects in the paroxetine group were headache, abdominal pain, nausea, respiratory disorder, somnolence, hyperkinesias, and trauma.

Atypical Antipsychotic Augmentation

Adjunctive risperidone ([?] 2 mg daily) was investigated in an open trial for 17 adolescents with OCD who did not respond to two serotonin reuptake inhibitor monotherapy trials. A significant reduction in CY-BOCS scores was reported (Thomsen 2004).

Aripiprazole augmentation of CBT was found to be effective in the case of an adolescent who had a partial response to combined CBT and sertraline (Storch *et al.* 2008). In a naturalistic sample of 220 children and adolescents with OCD, 43 children were treated with an atypical antipsychotic as an augmenting agent (Masi *et al.* 2009). Twenty-five of these youths (58.1%) responded to treatment.

The efficacy of aripiprazole augmentation of an SSRI was assessed in 39 youths with OCD who had not responded to two trials with SSRI monotherapy (Masi *et al.* 2010). Fifty-nine percent of the youths responded to treatment.

Other Agents

D-Cycloserine

Augmentation of CBT with D-cycloserine has been evaluated in three controlled trials with mixed results. D-Cycloserine augmentation of CBT was evaluated in a double-blind, placebo-controlled trial for 30 youths (ages 8-17 years) with OCD. No significant differences were found between treatment groups (Storch *et al.* 2010).

In a placebo-controlled randomized trial, 142 children and adolescents (ages 7-19 years) with OCD were randomly assigned to D-cycloserine plus CBT or placebo plus CBT (Storch *et al.* 2016). There were no additional benefits from D-cycloserine augmentation of CBT.

D-Cycloserine-augmented CBT was assessed in a double-blind, placebo-controlled pilot trial in 17 youths with difficult-to-treat OCD (Farrell *et al.* 2013). The augmented CBT resulted in greater improvement in OCD symptoms than CBT plus placebo.

Riluzole

Sixty children and adolescents with treatment-resistant OCD participated in a 12-week double-blind, placebo-controlled trial of add-on riluzole or placebo with current treatment (Grant *et al.* 2014). The riluzole final dosage was 100 mg/day. All participants significantly improved on CY-BOCS ratings, and there was no significant difference between riluzole and placebo on any outcome measure. Adverse events reported for patients given riluzole included one case of pancreatitis and five instances of slight increases in transaminases.

N-Acetylcysteine

N-acetylcysteine (NAC) augmentation of stable psychiatric treatment (both medication and therapy) was evaluated in a pilot double-blind, placebo-controlled 12-week trial in children and adolescents (ages 8-17 years) with OCD (Li *et al.* 2020). NAC dosages were up to 2,700 mg/day. Enrollment was stopped at 11 children out of 12 planned due to poor recruitment and study medication expiration. NAC was associated with a significant reduction in CY-BOCS total scores compared with placebo.

Meta-Analyses: Pharmacological Treatments

A systematic review of SSRIs for the treatment of OCD in children and adolescents included 12 RCTs with a total of 958 participants (Kotapati *et al.* 2019). SSRIs were shown to be superior to placebo, but effect sizes were small (standardized mean difference [SMD] = -0.43). In a different meta-analysis of pharmacological treatments for children and adolescents with OCD, the effect size for comparison of SSRIs with placebo was 0.51 (Ost *et al.* 2016).

A systematic review and meta-analysis of SSRIs and clomipramine that included nine RCTs involving 801 children and adolescents with OCD showed that the greatest benefit for SSRIs and clomipramine occurred early in treatment and that clomipramine had greater efficacy versus placebo than did SSRIs (Varigonda *et al.* 2016).

A systematic review and meta-analysis of fluoxetine in acute treatment of children and adolescents with OCD that included 188 participants in three RCTs of fluoxetine versus placebo and one RCT of fluoxetine versus citalopram was conducted (Maneeton *et al.* 2020). Fluoxetine was associated with significantly greater reduction in OCD severity, as measured by CY-BOCS, NIMH Obsessive Compulsive Scale, and CGI-S scores compared with placebo, although sample sizes were small.

Clinical Recommendations for Obsessive-Compulsive Disorder

SSRIs are the medication treatment of choice for OCD in children and adolescents (American Academy of Child and Adolescent Psychiatry 2012). Clomipramine is also effective in the treatment of this disorder; however, it is not a first-line treatment because of its adverse-event profile. A 12-week trial at an adequate dosage is indicated to determine whether a child with OCD will respond to an SSRI. If a child does not respond to one SSRI, switching to another SSRI is a reasonable strategy. Clomipramine, either as monotherapy or as augmentation of an SSRI, may be a third treatment option. Other possible SSRI augmentation strategies are clonazepam and atypical antipsychotics; however, these agents have not received systematic study. Some pediatric patients may need long-term medication maintenance; however, it is reasonable to attempt medication discontinuation 1 year after symptom stabilization. Medication should be tapered gradually to assess for relapse. Two or three relapses should lead to long-term treatment.

Posttraumatic Stress Disorder

The prevalence of PTSD in adolescents is reported to be 5% (Merikangas *et al.* 2010). The criteria for diagnosing PTSD in children older than age 6 years are the same as those used for adults (American Psychiatric Association 2013). PTSD symptoms in children tend to vary over time, and although the disorder is chronic, the course is prolonged with greater severity of the stressor (Clarke *et al.* 1993).

Selective Serotonin Reuptake Inhibitors

Sertraline

The efficacy of sertraline was evaluated in a 10-week double-blind, placebo-controlled trial of 131 children and adolescents with PTSD (Robb *et al.* 2010). Sertraline dosages ranged from 50 to 200 mg/day. There was no difference between sertraline-treated patients and placebo-treated patients in scores on the primary outcome measure, the University of California at Los Angeles Posttraumatic Stress Disorder Reaction Index for DSM-IV.

The benefit of adding sertraline versus placebo to trauma-focused CBT was assessed in a controlled 12-week trial (Cohen *et al.* 2007). Although both groups showed significant improvement in symptoms of PTSD, there was no significant advantage from adding sertraline rather than placebo to CBT.

Citalopram

Eight adolescents with PTSD received citalopram in a fixed daily dosage of 20 mg in a 12-week open-label study (Seedat *et al.* 2001). Core PTSD symptoms of reexperiencing, avoidance, and hyperarousal showed statistically significant improvement at week 12, with a 38% reduction in total score on the Clinician-Administered PTSD Scale-Child and Adolescent Version. Citalopram was well tolerated, and the most common side effects were increased sweating, nausea, headache, and tiredness.

In a larger 8-week open trial, Seedat *et al.* (2002) treated 24 children and adolescents with citalopram (dosage range = 20-40 mg/day; mean daily dosage = 20 mg). Both children and adolescents had a significant reduction in Clinician-Administered PTSD Scale-Child and Adolescent Version scores at endpoint. Common side effects of citalopram were drowsiness, headache, nausea, and increased sweating.

Alpha-2 Agonists

Guanfacine

The effectiveness of guanfacine extended release (XR) was assessed in an 8-week open-label trial for 19 youths (ages 6-18 years) with current traumatic stress symptoms (Connor *et al.* 2013). Guanfacine XR dosages ranged from 1 to 4 mg/day. On parent report, symptom clusters of reexperiencing, avoidance, and overarousal significantly improved.

Clonidine

Seven preschool children (ages 3-6 years) with a diagnosis of PTSD received open treatment with clonidine at a dosage range of 0.05-0.15 mg/day (Harmon and Riggs 1996). To decrease sedation, oral clonidine was subsequently converted to a clonidine patch. The majority of children showed at least moderate improvements in hyperarousal, hypervigilance, insomnia, nightmares, and mood lability.

Other Agents

Carbamazepine

Twenty-eight children and adolescents (ages 8-17 years) with a diagnosis of PTSD received carbamazepine (dosage range = 300-1,200 mg/day) for an average of 35 days. Twenty-two patients (78%) became asymptomatic, and the remaining six patients were significantly improved during the course of treatment (Looff *et al.* 1995).

Propranolol

The efficacy of propranolol initiated within 12 hours after emergency department admission in preventing PTSD in 29 injured youths was assessed in a 10-day double-blind, placebo-controlled trial (Nugent *et al.* 2010). There was no significant difference between the propranolol and placebo groups in PTSD symptoms at 6 weeks.

Eleven children (ages 6-12 years) with a diagnosis of PTSD participated in an off-on-off medication design of 4 weeks of propranolol treatment (Famularo *et al.* 1988). Propranolol was initiated at 0.8 mg/kg/day and titrated to a maximum of 2.5 mg/kg/day. A significant improvement in PTSD symptoms was found during the treatment period. Side effects included sedation and mildly lowered blood pressure and pulse.

Prazosin

A systematic review of prazosin in children and adolescents with PTSD included nine published articles, of which six were case reports. These case reports described improvement in patients receiving prazosin, with dosages ranging from 1 to 4 mg/day (Akinsanya *et al.* 2017).

D-Cycloserine

In a controlled trial, 57 youths (ages 7-18 years) with PTSD were randomly assigned to receive D-cycloserine and CBT or placebo and CBT (Scheeringa and Weems 2014). Although both groups had significant reductions in PTSD symptoms, there was no significant difference between the groups.

Risperidone

In case reports and a small open-label trial, risperidone has shown some benefit in reducing symptoms of PTSD in children and adolescents (Horrigan and Barnhill 1997; Keeshin and Strawn 2009; Meighen *et al.* 2007).

Quetiapine

In a case series, six adolescents with PTSD reported improvement in symptoms after 6 weeks of low-dosage (50-200 mg/day) quetiapine (Stathis *et al.* 2005).

Meta-Analysis: Psychological and Pharmacological Treatments

A meta-analysis of the efficacy of psychological and psychopharmacological treatment for PTSD in children and adolescents included 41 RCTs (39 psychological treatments, 2 psychopharmacological treatments) (Morina *et al.* 2016). Psychological interventions were found to be effective in treating PTSD, but there was very little evidence to support pharmacological treatment for PTSD in children and adolescents.

Clinical Recommendations for Posttraumatic Stress Disorder

To date, there are no FDA-approved medications for the treatment of children and adolescents with PTSD. The AACAP recommends considering SSRIs for pharmacological treatment of PTSD in children and adolescents. Other possible medications for PTSD are a- and b-adrenergic blocking agents, non-SSRI antidepressants, and mood-stabilizing agents (Cohen *et al.* 2010).

Attention-Deficit/Hyperactivity Disorder

The prevalence of ADHD in children and adolescents is estimated to range from 5% to 12%, whereas about 4% of adults in the general population meet criteria for ADHD (Kessler *et al.* 2006). In addition to demonstrating the core behavioral features of inattention, hyperactivity, and impulsivity, children with ADHD often have significant impairment in social and academic functioning (Barkley 2005). Of all of the childhood psychiatric disorders, ADHD has the greatest number of pharmacological treatment studies.

Psychostimulants

Stimulants have been used in child psychiatry for more than eight decades (Bradley 1937). Since the 1960s there have been hundreds of studies examining the effects of stimulants in children with ADHD; recently a major systematic review and network meta-analysis of double-blind, placebo-controlled trials of psychostimulants and other ADHD medications was published (Cortese *et al.* 2018). This meta-analysis examined effect sizes for both efficacy and side effects relative to placebo along with the 95% CI. In children and adolescents, the SMD for efficacy relative to placebo (based on clinician ratings) for amphetamine was -1.02 (95% CI: -1.19 to 0.85), and that of methylphenidate was -0.78 (95% CI: -0.93 to -0.62). Ratings of adverse events versus placebo significantly favored methylphenidate over amphetamine, leading the authors to suggest that methylphenidate was the preferred psychostimulant in children, but initial use of amphetamine remains appropriate.

Attention has turned to the study of potential long-term benefits of stimulant treatment of ADHD. It is not practical or ethical to do long-term placebo-controlled studies of ADHD medications. Increasingly, so-called big data studies can tie prescription of stimulants to other events in large databases, such as suicide rates, accidents, or arrests. These allow investigators to assess the impact of treatment over time. Relative to periods off medication (almost always stimulants), patients with ADHD on medication have fewer motor vehicle accidents (Chang *et al.* 2017) and traumatic brain injuries (Liao *et al.* 2018), are less likely to engage in criminal activity (Lichtenstein *et al.* 2012), and have lower rates of suicidal behavior (S. H. Liang *et al.* 2018) and substance abuse (Quinn *et al.* 2017).

The appendix at the end of this chapter shows the recommended dosage ranges for psychostimulants. The appendix also discusses adverse events, particularly growth suppression, that can occur with these medications.

Atomoxetine

Atomoxetine is a noradrenergic reuptake inhibitor that has indirect effects on dopamine reuptake in the cortex but not in the striatum (Bymaster *et al.* 2002). Numerous double-blind, placebo-controlled trials have demonstrated the medication's efficacy in the treatment of ADHD in children, adolescents, and adults (Michelson *et al.* 2001, 2002, 2003).

Atomoxetine is effective in treating ADHD in patients with comorbid tics and may also reduce tics (Allen *et al.* 2005). It is also useful for children with ADHD who have comorbid anxiety, showing effectiveness in treating anxiety and inattention (Sumner *et al.* 2005). Data from 13 (6 double-blind, 7 open-label) atomoxetine studies were pooled for youths (ages 12-18 years) with ADHD (Wilens *et al.* 2006). Of the 601 atomoxetine-treated subjects in this meta-analysis, 537 (89.4%) completed 3 months of acute treatment. At the time of the article's publication, 259 subjects (48.4%) were continuing atomoxetine treatment; 219 of these subjects had completed at least 2 years of treatment. Symptoms remained improved for up to 24 months without dosage escalation. During the 2-year treatment period, 99 subjects (16.5%) discontinued treatment due to lack of effectiveness, and 31 subjects (5.2%) discontinued treatment due to adverse events. No clinically significant abnormalities in height, weight, blood pressure, pulse, mean laboratory values, or electrocardiography parameters were found in atomoxetine-treated subjects.

Information about dosages, monitoring, and adverse effects of atomoxetine is provided in the appendix to this chapter.

Alpha-2 Adrenergic Receptor Agonists

Clonidine and guanfacine are both agonists at the a_2 receptor, which is found both presynaptically and postsynaptically in the brain. Activation of these receptors may underlie the therapeutic action of these agents in ADHD (Gamo *et al.* 2010). Guanfacine activates presynaptic a adrenoceptors 10 times more selectively than clonidine; guanfacine has an alpha a_2/a_1 receptor selectivity ratio 25 times higher than that of clonidine (Seedat 1985). As a result, clonidine is more potent than guanfacine and has a higher rate of inducing sedation. Hirota *et al.* (2014) performed a meta-analysis of all the placebo-controlled trials of clonidine and guanfacine in the treatment of ADHD.

Immediate-release clonidine was the subject of three trials involving 212 subjects. The mean dosage was 0.24 mg/day. In all three trials, clonidine was superior to placebo in reducing ADHD symptoms. Clonidine extended release was evaluated in a trial of 236 subjects at a mean dosage of 0.3 mg/day, and again clonidine was superior to placebo. Although guanfacine immediate release is commonly used in clinical practice, Hirota *et al.* (2014) found only one controlled study of its effects in ADHD; this study had only 34 participants, but guanfacine was found to be superior to placebo. In contrast, guanfacine XR has been studied in four double-blind, placebo-controlled studies involving more than 1,000 participants. The dosage range in the four studies was 2.5 to 3 mg/day, and all four studies showed guanfacine XR to be superior to placebo.

Hirota *et al.* (2014) combined all of the studies of clonidine and guanfacine to calculate the SMD of the a agonists versus placebo to be -0.59 for ADHD symptoms and -0.44 for symptoms of oppositional defiant disorder (ODD). Thus, the effect size of the a agonists is about one-half that of the psychostimulants.

Both clonidine (Kollins *et al.* 2011) and guanfacine (Wilens *et al.* 2012) have been studied as adjunctive treatments to psychostimulants for ADHD. These studies recruited participants with ADHD who had only a partial response to psychostimulants. Either an a_2 agonist or placebo was then added to the participants' stable psychostimulant dosage for several weeks in a double-blind fashion. In both studies, addition of the a agonist led to greater reduction in ADHD symptoms than addition of placebo. In a placebo-controlled comparison of dexmethylphenidate, guanfacine, and the two agents combined, the combination was superior to either agent alone in the treatment of ADHD (McCracken *et al.* 2016).

Information on the dosing of a_2 agonists and a discussion of side effects can be found in the appendix to this chapter.

Viloxazine

Viloxazine is a specific norepinephrine reuptake inhibitor, but in vivo studies in rodents (C. Yu *et al.* 2020) found that it increases serotonin, norepinephrine, and dopamine levels in the prefrontal cortex but does not increase dopamine in the nucleus accumbens, suggesting minimal abuse potential. C. Yu *et al.* (2020) also found that in vitro, viloxazine had antagonistic activity at serotonin type 2B receptors and agonistic activity at serotonin type 2C receptors, although the clinical relevance of this finding is not known.

An extended-release form of viloxazine was recently approved by the FDA for the treatment of ADHD. A randomized, double-blind, placebo-controlled 6-week trial assessed the efficacy and safety of once-daily 100 and 200 mg viloxazine in the treatment of ADHD in 477 male and female children 6-11 years of age (Nasser *et al.* 2020). At the end of the study, both dosages were superior to placebo in reducing symptoms on the ADHD Rating Scale-5.

Subsequently, Nasser *et al.* (2021) published a Phase III double-blind study of 200 and 400 mg of extended-release viloxazine versus placebo in 313 children ages 6-11 years diagnosed with ADHD. After 8 weeks, the change from baseline in the ADHD Rating Scale-5 was significantly greater in both the 200-and 400-mg groups compared with the placebo group. The 200-mg group separated from placebo at week 2, and both dosage groups separated from the placebo group at weeks 5-8.

Information on the dosing and side effects of viloxazine is provided in the appendix at the end of this chapter.

Clinical Recommendations for Attention-Deficit/Hyperactivity Disorder

Selection of an agent to treat ADHD should be based on the needs of the individual patient and family preference. Based on the strength of clinical trial data, stimulants have the largest effect size for the treatment of ADHD and are often the first agents used, but either atomoxetine, guanfacine, or viloxazine can also be used. Because of its sedating effect, clonidine is used only when the above agents have failed. Substantial numbers of patients have only a partial response to psychostimulants; multiple studies have shown that adding an a_2 agonist to the psychostimulant is an effective way to achieve a greater reduction in ADHD symptoms.

Disruptive Behavior Disorders, Mood Lability, and Aggression

ODD and conduct disorder are highly comorbid with ADHD, particularly in younger children (Pliszka 2009). DSM-5 added the diagnosis of disruptive mood dysregulation disorder (DMDD) in the Depressive Disorders category of the manual. Children with DMDD show chronically irritable mood combined with frequent outbursts of verbal and physical aggression. Children with DMDD may not meet criteria for bipolar disorder, but they may meet criteria for MDD. Psychopharmacological studies have looked at groups of children (principally with ADHD) who show high levels of aggression as a symptom, as well as those with diagnoses of DMDD. Treatments for ADHD have been used to target ODD and conduct disorder, whereas mood stabilizers and antipsychotics have been used for patients with severe aggressive outbursts, regardless of diagnosis (Pappadopulos *et al.* 2006).

ADHD With Aggression

Psychostimulants and Behavior Treatment Alone

In a meta-analysis of the literature from 1970 to 2001 that examined 28 studies to determine the effect size for stimulants on overt and covert aggression-related behaviors in children with ADHD, it was found that the mean effect size for aggressive behaviors was similar to that for core behaviors of ADHD (Connor *et al.* 2002). Two major studies (Aman *et al.* 2014; Blader *et al.* 2021) showed that adding parent training to psychostimulants can significantly reduce aggression in children with ADHD.

Combining Psychostimulants With Alpha-2 Agonists

Children (ages 6-14 years) with ADHD currently taking methylphenidate were randomly assigned to receive clonidine syrup 0.10-0.20 mg/day (*n* =

37) or placebo (*n* = 29) for 6 weeks (Hazell and Stuart 2003). Analysis showed that significantly more clonidine-treated children than control subjects were responders on the Conduct subscale (21 of 37 vs. 6 of 29; $P < 0.01$) of the parent-report Conners Behavior Checklist but not on the Hyperactive Index subscale (13 of 37 vs. 5 of 29). Compared with placebo, clonidine was associated with a greater reduction in systolic blood pressure measured standing and with transient sedation and dizziness. Clonidine-treated children had a greater reduction in a number of unwanted effects associated with psychostimulant treatment compared with placebo. The findings supported the use of clonidine in combination with psychostimulant medication to reduce conduct symptoms associated with ADHD.

Although no studies have specifically examined the effect of guanfacine on aggression in children with ADHD, controlled trials of guanfacine have shown that it clearly reduces symptoms of ODD (Hirota *et al.* 2014), and thus it is common practice to combine guanfacine with psychostimulants to treat aggression in children and adolescents with ADHD.

Combining Psychostimulants With Antipsychotics or Mood Stabilizers

Aman *et al.* (2014) tested the efficacy of adding risperidone to concurrent psychostimulant treatment and parent training (PT) in behavior management in children with ADHD and severe comorbid aggression. Children ages 6-12 years (mean age 8.89 years) with severe physical aggression were randomly assigned to a 9-week trial of PT, stimulant, and placebo (basic treatment; *n* = 84) or of PT, stimulant, and risperidone (augmented treatment; *n* = 84). Children received a psychostimulant for 3 weeks, titrated for optimal effect, while parents received PT. If there was room for improvement at the end of week 3, placebo or risperidone was added for an additional 3 weeks. Both groups showed substantial reductions in aggressive behavior during the first 3 weeks of stimulant plus PT treatment. In the second phase, the risperidone group showed significantly greater reduction in rating scale measures of aggressive behavior, but CGI-I scores did not discriminate the groups. Adverse events were as expected, with the risperidone group experiencing greater weight gain and increases in serum lipid and prolactin levels than the placebo group.

Blader *et al.* (2009) treated 74 children with ADHD and aggression with open stimulant treatment during a lead-in phase that averaged 5 weeks. Children whose aggressive behavior persisted at the conclusion of the lead-in phase (*n* = 30) were randomly assigned to receive double-blind, flexibly dosed divalproex or a placebo adjunctive to stimulant for 8 weeks. Families received weekly behavioral therapy throughout the trial. A significantly higher proportion of the children randomly assigned to divalproex met remission criteria (8 of 14; 57%) than of those randomly assigned to placebo (2 of 13; 15%).

Blader *et al.* (2021) enrolled 151 children ages 6-12 years with ADHD and significant aggressive behavior in an open, systematically titrated stimulant trial. Afterward, participants who showed an inadequate reduction in aggressive behavior were randomly assigned to receive adjunctive risperidone, divalproex, or placebo under double-blind conditions for 8 weeks. Family-based behavioral treatment was offered throughout the trial. Aggression remitted among 96 (63%) of the participants in the first phase of the trial, and among the remaining participants, 45 were then randomly assigned to receive adjunctive risperidone, divalproex, or placebo. Both the risperidone and divalproex groups showed significantly greater reductions in aggression than the placebo group; those in the risperidone group showed the greatest weight gain.

Treating Aggression Without ADHD

In the following older studies, meeting criteria for ADHD was not a requirement for study entry, and there was no psychostimulant treatment before the agent for aggression was administered.

Lithium

The efficacy of lithium in the treatment of aggression in youths with CD has been demonstrated in three double-blind, placebo-controlled inpatient studies (Campbell *et al.* 1984, 1995; Malone *et al.* 2000). In these studies, lithium was titrated to serum levels of 1-1.2 mEq/L. Lithium was superior to placebo in all three studies, with the most common lithium side effects being stomach ache, nausea, vomiting, headache, tremor, and urinary frequency.

Divalproex

Steiner *et al.* (2003) randomly assigned 71 adolescents with conduct disorder in a residential facility for juvenile offenders to two groups, which received either a therapeutic dosage or a low dosage of divalproex for 7 weeks; both subjects and outcome raters were blind to treatment status. Reduction in aggression severity, improvement in impulse control, and global improvement were greater in the group with therapeutic divalproex levels than in the low-dosage condition.

Disruptive Mood Dysregulation Disorder

Although the above studies probably included participants with DMDD, only a few treatment studies have enrolled participants who specifically met criteria for this disorder. Dickstein *et al.* (2009) studied the effect of lithium in youths (ages 7-17 years) with severe mood dysregulation who were tapered off their medications. Those who continued to have significant mood dysregulation after a 2-week single-blind placebo run-in were randomly assigned to a 6-week double-blind trial of either lithium (*n* = 14) or placebo (*n* = 11). Interestingly, 20 of 45 youths (45%) with severe mood dysregulation

were not randomly assigned to treatment because of significant clinical improvement during the placebo run-in. In the 6-week double-blind trial, there were no significant between-group differences on any clinical measures. The placebo group showed no improvement at all (a true negative trial), with no evidence that an increase in sample size would have changed the results.

In DSM-5, DMDD was included with the Depressive Disorders rather than with Bipolar and Related Disorders, in part because of studies showing that children with DMDD showed the onset of major depressive episodes rather than manic episodes later in life (Stringaris *et al.* 2010), raising the question of whether DMDD would respond to antidepressant treatment. A group of 49 children ages 7-17 years (mean age 11.4 years) were treated with methylphenidate and then randomly assigned in a double-blind fashion to either adjunctive citalopram or placebo for 8 weeks (Towbin *et al.* 2020). At the end of the trial, response was seen in a significantly higher proportion of participants assigned to the combination (35%) than in those assigned to stimulant with placebo (6%). Almost two-thirds of the citalopram groups did not respond, however, and the authors noted that there was no difference in measures of functional impairment.

Although risperidone has been shown to be effective in aggression (Aman *et al.* 2014; Blader *et al.* 2021), only one open trial of risperidone has been done in children with DMDD. Twenty-one ($n = 21$) participants with severe mood dysregulation were enrolled in an 8-week trial in which risperidone was titrated from 0.5 to 3 mg/day over the first 2 weeks (Krieger *et al.* 2011). By end of study at 8 weeks, there was a significant reduction in the Irritability subscale of the Aberrant Behavior Checklist (ABC).

Clinical Recommendations for Disruptive Behavior Disorders and Aggression

The Center for the Advancement of Children's Mental Health at Columbia University joined with the New York State Office of Mental Health to develop guidelines for treatment of aggression, which led to the Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (Pappadopulos *et al.* 2003; Schur *et al.* 2003). These recommendations call first for a thorough psychiatric evaluation of the child with severe aggression. Next, a psychosocial intervention should be used first when the aggression is the primary problem, such as in ODD, conduct disorder, or intermittent explosive disorder. The clinician should then treat any primary condition, such as ADHD, psychosis, or mood disorder, that may be causing or contributing to the aggression.

a_2 Agonists may be used for children with milder aggression or temper outbursts because the effect size of these medications on aggression is more modest (Hazell and Stuart 2003). An SSRI may be considered for patients with DMDD, particularly if prominent depressive symptoms are present (Towbin *et al.* 2020). If the aggression does not respond to these steps, then an atypical antipsychotic should be used. Different atypical antipsychotics should be tried as monotherapy before polypharmacy is tried (Pliszka 2009).

Tourette Syndrome

The prevalence of Tourette syndrome is estimated to be 0.7% in children (Comings *et al.* 1990). Tourette syndrome is characterized by multiple motor tics and by one or more vocal tics that occur frequently for longer than 1 year. More commonly, children have chronic motor or vocal tics, but treatment is the same as for Tourette syndrome.

Alpha-2 Adrenergic Receptor Agonists

Weisman *et al.* (2013) identified six placebo-controlled studies examining the effects of clonidine or guanfacine in patients with tics. A meta-analysis of these studies demonstrated a significant effect of a_2 agonists relative to placebo, with an SMD of 0.31 (95% CI, 0.15-0.48).

Antipsychotics

Weisman *et al.* (2013) reviewed five placebo-controlled studies of haloperidol, pimozide, ziprasidone, and risperidone. Two studies directly compared haloperidol and risperidone without a placebo control (Bruggeman *et al.* 2001; Gilbert *et al.* 2004), one study compared risperidone and clonidine (Gaffney *et al.* 2002), and one study compared haloperidol and the clonidine patch (Kang *et al.* 2009). In the meta-analysis, all antipsychotics were superior to placebo, with an SMD of 0.61 (95% CI, 0.36-0.86). There was no difference between the various antipsychotic agents with regard to their efficacy for reducing tics. Gaffney *et al.* (2002) found clonidine and risperidone to be equivalent in efficacy.

Murphy *et al.* (2005) reported on six cases of children and adolescents (age range = 8-19 years; mean age = 12.1 years) who had comorbid tic disorder and OCD and were treated with aripiprazole (mean dosage = 11.7 mg/day; range = 5-20 mg/day) for 12 weeks. The subjects experienced a mean reduction of 56% in the severity of their tics as assessed by the Yale Global Tic Severity Scale. Similarly, Yoo *et al.* (2006) treated 15 children and adolescents who had tic disorder with aripiprazole (mean dosage = 10.89 mg/day; range = 2.5-15 mg/day) and reported a mean reduction of 40% in Yale Global Tic Severity Scale scores; side effects were minimal. Two subjects experienced nausea, one experienced weight gain, and one experienced sedation. The sedation responded to dosage reduction.

In a case series, 11 consecutive patients with Tourette syndrome (mean age = 7 years; age range = 7-50 years) were treated with aripiprazole; the symptoms of the majority of these patients had been refractory to previous treatments with other antipsychotics (Davies *et al.* 2006). Ten of the 11 patients who were treated with aripiprazole improved, although to variable degrees. In the majority of patients, response was sustained with aripiprazole dosages ranging from 10 to 20 mg/day. Side effects were mild and transient. Zheng *et al.* (2016) reviewed six studies of the treatment of tics with aripiprazole. This study included two RCTs, but in these studies aripiprazole was compared only with tiapride, an antipsychotic not available in the United States. The other four studies were open trials. The review found aripiprazole to be well tolerated and effective in reducing tics relative to baseline levels.

Clinical Recommendations for Tourette Syndrome

The American Academy of Neurology has recently published guidelines for the treatment of Tourette syndrome (Pringsheim *et al.* 2019). The guidelines emphasized that if a tic is not severe or socially impairing, observation may be in order because tics typically wax and wane; in general, tics improve over time. The Comprehensive Intervention for Tics is a highly effective habit reversal treatment for tics; it should always be considered before medication is started (Woods *et al.* 2008). If conservative treatment fails, use of an a_2 agonist would be the first stage of medication treatment. Only if a agonists fail (and Comprehensive Intervention for Tics has not worked or is not available) should antipsychotics be considered. The American Academy of Neurology guidelines (Pringsheim *et al.* 2019) recommend individualizing the choice of first-or second-generation antipsychotics as the first choice, noting that the clinician should balance the risks and benefits of each class.

Although tics are known rare side effects of psychostimulants, it is of interest that in a double-blind, placebo-controlled study of methylphenidate, clonidine, and a combination of the two medications for children with comorbid ADHD and tic disorders, methylphenidate did not exacerbate tics. The best response of both the ADHD symptoms and the tics was found in the combined group (Tourette's Syndrome Study Group 2002). Atomoxetine was also found to reduce tics in patients with both ADHD and tic disorders (Allen *et al.* 2005). Thus, psychostimulants can be combined with a_2 agonists to control both ADHD and tics in patients with both disorders.

Schizophrenia

Cases of schizophrenia in children younger than age 13 years are very rare; however, the prevalence rises in adolescence, with peak onset between ages 15 and 30 years (McClellan and Werry 2001). The clinical features of the disorder are similar in youth and adults, and the same DSM-5 criteria are used to establish a diagnosis. Childhood-onset schizophrenia is associated with substantial impairment from positive and negative symptoms (Stentebjerg-Olesen *et al.* 2016).

Atypical Antipsychotics

Six atypical antipsychotics have FDA approval for the treatment of schizophrenia in adolescents: olanzapine (for ages [?] 13 years), risperidone ([?] 13 years), aripiprazole ([?] 13 years), quetiapine ([?] 13 years), paliperidone ER ([?] 12 years), and lurasidone ([?] 13 years). Ziprasidone, asenapine, and clozapine have been studied for treatment of schizophrenia in youths but do not have FDA approval. Information about dosages, monitoring, and adverse effects of atypical antipsychotics is provided in the appendix to this chapter.

Olanzapine

In a double-blind, placebo-controlled multicenter investigation of olanzapine (mean dosage = 11.1 mg/day) for the treatment of adolescents with schizophrenia (Kryzhanovskaya *et al.* 2009), 107 adolescents were randomly assigned to receive olanzapine (*n* = 72) or placebo (*n* = 35) for a 6-week trial. Olanzapine-treated adolescents had significantly greater improvements on the Brief Psychiatric Rating Scale for Children (BPRS-C) and in CGI-S scores compared with the placebo group. There was no significant difference in response rate (defined as a [?] 30% decrease in BPRS-C and a CGI-S score [?] 3) between the olanzapine (37.5%) and placebo (25.7%) groups. Significantly more olanzapine-treated adolescents had high aspartate aminotransferase/serum glutamic oxaloacetic transaminase. alanine aminotransferase/serum glutamic pyruvic transaminase, and prolactin levels, as well as low bilirubin levels and hematocrit values, during treatment. There was a significant increase in fasting triglycerides at endpoint in the olanzapine-treated adolescents. Early response at 2 and 3 weeks has been shown to predict ultimate response and remission at week 6 (Stentebjerg-Olesen *et al.* 2015).

Risperidone

Positive findings were reported in a double-blind, placebo-controlled multicenter trial of risperidone in the treatment of adolescents with schizophrenia (Haas *et al.* 2009b). One hundred sixty adolescents were randomly assigned to risperidone 1-3 mg/day (*n* = 55), risperidone 4-6 mg/day (*n* = 51), or placebo (*n* = 54) for a 6-week trial. Both dosage ranges of risperidone were significantly superior to placebo on the primary efficacy measure, the Positive and Negative Syndrome Scale (PANSS) total change score at endpoint. The most common adverse events in the risperidone 1-to 3-mg/day group were somnolence (24%), agitation (15%), and headache (13%). EPS (16%), dizziness (14%), and hypertonia (14%) were the most common adverse events in the risperidone 4-to 6-mg/day group. The investigators concluded that the overall risk-benefit ratio favored the lower dosage range of risperidone.

Aripiprazole

In a large double-blind, placebo-controlled multicenter trial of aripiprazole for the treatment of schizophrenia in adolescents (Findling *et al.* 2008), 302 adolescents were randomly assigned to receive aripiprazole 10 mg/day, aripiprazole 30 mg/day (after 5-or 11-day titration), or placebo over a 6-week period. Both dosages of aripiprazole led to statistically significant differences from placebo on the PANSS total score at week 6. The most common adverse events associated with aripiprazole were EPS, somnolence, and tremor. Early response to aripiprazole at weeks 2 and 3 has been shown to predict later response and remission (Correll *et al.* 2013).

Aripiprazole as maintenance treatment for adolescent schizophrenia was evaluated in a 52-week randomized, placebo-controlled withdrawal study (Correll *et al.* 2017). A total of 146 youths were randomly assigned to aripiprazole (n = 98) or placebo (n = 48) in the double-blind maintenance phase. Aripiprazole-treated youths had a significantly longer time to exacerbation of psychotic symptoms or impending relapse than placebo-treated youths (hazard ratio: 0.46).

Quetiapine

The efficacy of quetiapine in the treatment of schizophrenia in adolescents was evaluated in a 6-week double-blind, placebo-controlled trial in which subjects (N = 222) were randomly assigned to quetiapine 400 mg/day, quetiapine 800 mg/day, or placebo (Findling *et al.* 2012a). Both quetiapine dosages were significantly superior to placebo in reduction of total PANSS scores. The most common adverse events with quetiapine were somnolence, headache, and dizziness. Mean changes in body weight, total cholesterol, and total triglycerides were greater in the quetiapine groups than the placebo group.

Paliperidone Extended Release

Paliperidone ER was evaluated in a 6-week double-blind, placebo-controlled trial of 201 adolescents (ages 12-17 years) with schizophrenia (Singh *et al.* 2011). Paliperidone ER fixed dosing was weight based; youth weighing 29 kg to less than 51 kg received 1.5, 3, or 6 mg/day, whereas patients weighing at least 51 kg received 1.5, 6, or 12 mg/day. With weight-based treatment, only the medium dosage range (3-6 mg/day) led to significant improvement compared with placebo. The fixed dosages of 3, 6, and 12 mg/day were also superior to placebo. Somnolence, akathisia, insomnia, headache, and tremor were the most common adverse events in the paliperidone ER group.

The long-term safety of paliperidone ER was evaluated in a 2-year open-label study for 400 adolescents with schizophrenia (Savitz *et al.* 2015). The most frequently reported treatment-emergent adverse events were increased weight, headache, insomnia, nasopharyngitis, akathisia, schizophrenia exacerbation, and tremor. There were no clinically significant changes in weight or BMI. Hyperprolactinemia was found in 56% of patients, and 9.3% had prolactin-related adverse events. The most common EPS-related adverse events were parkinsonism (15.5%) and hyperkinesia (13.8%).

Ziprasidone

The efficacy of ziprasidone was evaluated in a 6-week double-blind, placebo-controlled trial for 283 adolescents ages 13-17 years with schizophrenia (Findling *et al.* 2013a). Ziprasidone was flexibly dosed (40-160 mg/day). There was no significant difference between ziprasidone and placebo on change from baseline to endpoint on the BPRS-Anchored. The most common adverse events in the ziprasidone group were somnolence and EPS. During the 26-week open-label follow-up, there were no clinically significant changes in metabolic indices and laboratory measures.

Asenapine

The efficacy of asenapine was assessed in an 8-week double-blind, placebo-controlled trial for adolescents ages 12-17 years with schizophrenia (Findling *et al.* 2015c). Asenapine dosing was 2.5 mg bid or 5 mg bid. Asenapine was not significantly superior to placebo on the primary efficacy measure of change from baseline to endpoint on the PANSS total score. Weight gain of 7% or greater, somnolence, sedation, and hypersomnia were more common in the asenapine group than the placebo group. Adverse events of akathisia, fasting glucose elevation, and EPS were more common in the asenapine 5 mg bid group than the placebo group. Youths who showed improvement during the acute phase maintained improvement in the 26-week open-label extension.

Lurasidone

Lurasidone was evaluated in a 6-week double-blind, placebo-controlled trial of 326 adolescents (ages 13-17 years) with schizophrenia (Goldman *et al.* 2017). Lurasidone dosage was fixed (40 or 80 mg/day). A significantly higher proportion of youths treated with lurasidone 40 mg/day and 80 mg/day than placebo-treated youths met responder criteria. The most common adverse events with lurasidone were nausea, somnolence, akathisia, vomiting, and sedation.

Youths who continued open-label lurasidone treatment showed continued improvement over a 2-year period (Correll *et al.* 2022). There were minimal effects on body weight, lipids, glycemic indices, and prolactin.

Clozapine

A 6-week double-blind, placebo-controlled comparison of clozapine and haloperidol was conducted in 21 children and adolescents (ages 6-18 years) with schizophrenia (Kumra *et al.* 1996). Clozapine (mean dosage = 176 mg/day; range = 25-525 mg/day) was significantly superior to haloperidol (mean dosage = 16 mg/day; range = 7-27 mg/day) in reducing positive and negative symptoms of schizophrenia. Clozapine improved interpersonal functioning and enabled patients to live in a less restrictive setting. However, side effects were significant with clozapine. One patient had a seizure, and three patients were given anticonvulsants after they became more irritable and aggressive and experienced epileptiform changes on electroencephalogram. Mild to moderate neutropenia, weight gain, and sinus tachycardia were the other major side effects.

Comparison of Atypical Antipsychotics

In a 12-week open-label trial, risperidone (mean dosage = 1.6 mg/day) was compared with olanzapine (mean dosage = 8.2 mg/day) in the treatment of 25 children with schizophrenia (Mozes *et al.* 2006). Both treatment groups showed similar, significant improvement as measured by PANSS total and subscale scores.

In an 8-week double-blind study, 50 children and adolescents (ages 8-19 years) with psychotic disorders were randomly assigned to receive risperidone (mean dosage = 4 mg/day), olanzapine (mean dosage = 12.3 mg/day), or haloperidol (mean dosage = 5 mg/day) (Sikich *et al.* 2004). Eighty-eight percent of patients treated with olanzapine, 74% treated with risperidone, and 53% treated with haloperidol met response criteria (CGI-I scores of much or very much improved and at least a 20% reduction in BPRS-C total score).

Clozapine was compared with olanzapine in an 8-week double-blind randomized trial (Shaw *et al.* 2006). Twenty-five youths (ages 7-16 years) with schizophrenia that was resistant to treatment with at least two antipsychotics participated in the trial. Clozapine (mean dosage = 327 mg/day) led to significant improvement on all outcome measures, whereas olanzapine (mean dosage = 19.1 mg/day) led to improvement on some outcome measures. Improvement in negative symptoms was significantly greater for the clozapine group.

In an 8-week double-blind trial comparing olanzapine and risperidone against the typical antipsychotic molindone in 116 children and adolescents with early-onset schizophrenia or schizoaffective disorder (Sikich *et al.* 2008), no significant differences were observed in rates of response (CGI-I score [?] 2 and [?] 20% reduction in PANSS total score) among the treatment groups (risperidone 46%, olanzapine 34%, and molindone 50%). Significantly greater weight gain occurred with olanzapine and risperidone than with molindone.

A double-blind maintenance study followed this acute controlled trial of children and adolescents with early-onset schizophrenia or schizoaffective disorder (Findling *et al.* 2010). Of the 54 youths eligible for the maintenance phase, 14 (26%) completed 44 weeks of treatment. No significant differences were found between olanzapine, risperidone, and molindone in reduction of symptoms or time to discontinuation.

In an 8-week double-blind trial comparing paliperidone ER and aripiprazole in 228 adolescents with schizophrenia (Savitz *et al.* 2015), there was no significant difference between the paliperidone ER group and the aripiprazole group on change in PANSS scores from baseline to endpoint. Both medication groups showed improvement in symptoms and functional outcomes.

The efficacy of quetiapine extended release versus aripiprazole was compared in 231 youths (ages 12-17 years) with schizophrenia spectrum and other psychotic disorders in a 12-week multicenter trial (Pagsberg *et al.* 2017a). There were no significant differences in outcome ratings (change in PANSS positive score from baseline to endpoint) between the quetiapine and the aripiprazole groups.

Typical Antipsychotics

Haloperidol

Haloperidol has been compared with placebo and other typical antipsychotics in controlled trials in youths. In a 10-week double-blind, placebo-controlled crossover study, the safety and efficacy of haloperidol were assessed in 12 hospitalized children (ages 5-12 years) with schizophrenia. Haloperidol (optimal dosage range = 0.5-3.5 mg/day) was significantly superior to placebo in improving overall clinical functioning and reducing ideas of reference, delusions, and hallucinations. Common side effects were acute dystonic reaction, drowsiness, and dizziness (Spencer *et al.* 1992).

Haloperidol and loxapine were compared in a 4-week double-blind, placebo-controlled study of 75 adolescent inpatients with schizophrenia. Both haloperidol and loxapine were significantly superior to placebo, and there was no significant difference in efficacy between the two medications. Response rates (based on CGI-I scores) were 87.5% for loxapine, 70% for haloperidol, and 36.4% for placebo. Common side effects were sedation, EPS, and somnolence (Pool *et al.* 1976).

Thiothixene

Thiothixene was compared with thioridazine in a 6-week single-blind study of 21 adolescent inpatients with schizophrenia. Thiothixene (optimal mean dosage = 16.2 mg/day) and thioridazine (optimal mean dosage = 178 mg/day) were equally effective in controlling symptoms, although most of the adolescents continued to be quite impaired. Thiothixene was less sedating than thioridazine (Realmuto *et al.* 1984). Thiothixene was also compared with trifluoperazine in an 8-week double-blind study of 16 children (ages 8-15 years) with schizophrenia (Wolpert *et al.* 1967). The effects of both medications were similar in terms of decreasing avoidance behavior, reducing stereotypic behavior, and increasing peer socialization.

Meta-Analyses: Pharmacological Treatments

A systematic review and network meta-analysis of antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, and ziprasidone) for treatment of schizophrenia spectrum disorders in children and adolescents showed comparable efficacy among antipsychotics for early-onset schizophrenia, except that efficacy appeared inferior for ziprasidone and unclear for asenapine (Pagsberg *et al.* 2017b).

A network meta-analysis of antipsychotics for treatment of children and adolescents showed clozapine was significantly more effective than other antipsychotics, but ziprasidone showed no efficacy (Krause *et al.* 2018).

Clinical Recommendations for Schizophrenia

Both typical and atypical antipsychotics have demonstrated effectiveness in the treatment of schizophrenia in youths, although the sample sizes have been small in the trials of typical antipsychotics. Because fewer EPS and instances of tardive dyskinesia have been reported with atypical antipsychotics, it would be reasonable to initiate treatment with an atypical antipsychotic for a child with schizophrenia. It is important to monitor weight and metabolic parameters for children who receive atypical antipsychotics. Clozapine should be considered for treatment-resistant schizophrenia (McClellan *et al.* 2013).

Antipsychotics should be administered at adequate dosages for a period of 6 weeks to assess efficacy. If there is no response or if intolerable side effects occur, a trial of a different antipsychotic should be initiated (American Academy of Child and Adolescent Psychiatry 2012).

There are limited data to guide maintenance treatment. Because the majority of youths will have a second psychotic episode within 5-7 years of stabilization, there is a significant risk of relapse with medication withdrawal (Kumra 2000). Maintenance treatment should be provided to most youths with schizophrenia to improve functioning and prevent relapse (American Academy of Child and Adolescent Psychiatry 2012). The aim is to use the lowest effective dosage of medication to reduce the risk of adverse events. For youths with prolonged remission, it may be possible to discontinue medication, but long-term monitoring will be necessary because of possible reemergence of psychotic symptoms.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a new DSM-5 disorder that encompasses the previous DSM-IV categories of autistic disorder (autism), Asperger's disorder, and pervasive developmental disorder not otherwise specified. Symptoms of ASD represent a continuum of mild to severe impairments in two core domains: deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests, and activities (American Psychiatric Association 2013). Associated behavioral features include hyperactivity, stereotypies, attentional problems, self-injurious behavior, aggression, mood lability, anxiety, obsessions, and compulsions. ASD is estimated to have a prevalence of up to 18.5 per 1,000 population (Maenner *et al.* 2020). The majority of children with the disorder will continue to have significant social and communication impairments throughout adulthood (Bieleninik *et al.* 2017).

Atypical Antipsychotics

For the treatment of irritability associated with ASD, the FDA has approved risperidone (for patients age [?] 5 years) and aripiprazole (age [?] 6 years). Lurasidone, olanzapine, quetiapine, and ziprasidone have been studied for ASD but do not have FDA approval for use by youths. Information about dosages, monitoring, and adverse effects of atypical antipsychotics is provided in the appendix to this chapter.

Risperidone

One hundred one children (ages 5-17 years) with DSM-IV-defined autistic disorder participated in an 8-week double-blind, placebo-controlled trial of risperidone (dosage range = 0.5-3.5 mg/day; mean dosage= 1.8 mg/day) (McCracken *et al.* 2002). A significantly greater positive response (defined as a 25% decrease on the Irritability subscale of the ABC and a rating of much or very much improved on the CGI-I) was found for the risperidone group (69%) than the placebo group (12%). Adverse events of increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group. Mean weight gain was 2.7 kg in the risperidone group and 0.8 kg in the placebo group. An 18-month follow-up showed that the majority of subjects who responded to risperidone during intermediate-length treatment continued to show improvement (McDougle *et al.* 2005).

In a 24-month follow-up of 84 of these youths, there was continued improvement in maladaptive behavior from baseline (Aman *et al.* 2015). Social skills improved and irritability decreased for youths who were taking risperidone at follow-up. Risperidone treatment was associated with enuresis, excessive appetite, and weight gain.

In an 8-week double-blind, placebo-controlled trial, 79 children (ages 5-12 years) with a DSM-IV diagnosis of autistic or other pervasive developmental disorder were randomly assigned to receive either placebo or risperidone (mean dosage = 1.5 mg/day). Risperidone-treated patients exhibited a 64% improvement over baseline irritability, compared with a 30.7% improvement in subjects receiving placebo (Shea *et al.* 2004).

In a 6-month placebo-controlled study of 40 children (ages 2-9 years) with autism, risperidone (1 mg/day) decreased aggressiveness, hyperactivity, and irritability and improved social responsiveness and nonverbal communication. Appetite increase, weight gain, sedation, and transient dyskinesias were reported in the risperidone-treated children (Nagaraj *et al.* 2006).

The long-term effects of risperidone were assessed in youths (ages 5-17 years) with ASD (Troost *et al.* 2005). Twenty-four youths received risperidone for 6 months, followed by a double-blind discontinuation to placebo or continued risperidone. Risperidone was superior to placebo in preventing relapse, with relapse rates of 25% and 75%, respectively.

In a double-blind, placebo-controlled risperidone dosing study in 96 youths (ages 5-17 years), high-dosage risperidone (1.25 mg/day for youths weighing 20 to < 45 kg; 1.75 mg/day for youths weighing [?] 45 kg) was significantly superior to placebo in baseline-to-endpoint change in score on the ABC Irritability subscale (Kent *et al.* 2013b). However, there was no significant difference between scores of patients given low-dosage risperidone (0.125 mg/day for youths weighing 20 to < 45 kg; 0.175 mg/day for youths weighing [?] 45 kg) and scores of patients given placebo. In an open-label extension study with flexibly dosed risperidone, all groups showed additional improvement in efficacy scores (Kent *et al.* 2013a).

The comparative efficacy of risperidone and haloperidol was assessed in an 8-week double-blind trial that included 30 children and adolescents with DSM-IV autistic disorder (Miral *et al.* 2008). Risperidone produced significantly greater reductions in scores on the ABC as well as on other scales used to assess symptoms of autism. An open-label continuation study (Gencer *et al.* 2008) of this controlled trial showed that risperidone-treated patients had greater improvement than haloperidol-treated patients on CGI ratings and on the ABC.

In a 24-week randomized trial, combined treatment with risperidone and PT was compared with risperidone alone for the treatment of severe behavioral problems in 124 children with ASD (Scahill *et al.* 2012). Combined treatment was superior to medication alone in reduction of noncompliant behavior as assessed by the Home Situation Questionnaire. In a 1-year follow-up, there was no significant difference between treatment groups on noncompliant behavior (Arnold *et al.* 2012).

Aripiprazole

The efficacy of aripiprazole in the treatment of irritability was evaluated in 218 children and adolescents with DSM-IV autistic disorder in an 8-week double-blind, placebo-controlled

trial (Marcus *et al.* 2009). Aripiprazole dosages were 5, 10, or 15 mg/day. Compared with placebo, all aripiprazole dosages produced significantly greater improvement in mean scores on the ABC Irritability subscale. The most common adverse events were sedation, tremor, and somnolence. The efficacy of aripiprazole was assessed in another 8-week double-blind, placebo-controlled trial that included 98 children and adolescents with DSM-IV autistic disorder (Owen *et al.* 2009). Aripiprazole dosages were 5, 10, or 15 mg/day. Significantly greater improvements in mean scores on the ABC Irritability subscale were seen with aripiprazole versus placebo. Rates of EPS-related adverse events were 14.9% with aripiprazole and 8% with placebo.

Aripiprazole was also shown to be significantly superior to placebo on the ABC (Japanese version) Irritability subscale score in an 8-week double-blind, placebo-controlled study of 92 children and adolescents (ages 6-17 years) with ASD in Japan (Ichikawa *et al.* 2017).

Long-term maintenance treatment with aripiprazole was examined in a double-blind, placebo-controlled relapse prevention trial for 86 youths with ASD (Findling *et al.* 2014). There was no statistically significant difference in time to relapse between aripiprazole and placebo. Relapse rates at week 16 were 35% for the aripiprazole group and 52% for the placebo group.

The efficacy of aripiprazole versus risperidone was compared in a 2-month randomized, double-blind trial that included 59 children and adolescents with ASD (Ghanizadeh *et al.* 2014). Both aripiprazole and risperidone groups had lower scores on the ABC at endpoint than at baseline; there was no statistically significant difference between these medications.

In a 10-week double-blind parallel-group study, 80 children and adolescents (ages 6-17 years) with ASD were randomly assigned to aripiprazole or risperidone. All participants significantly improved on the ABC Irritability subscale after 1 week and continued to improve for the remaining 9 weeks (DeVane *et al.* 2019).

Lurasidone

The efficacy of lurasidone for the treatment of irritability was evaluated for 150 children and adolescents (ages 6-17 years) in a 6-week double-blind placebo-controlled trial (Loebel *et al.* 2016). Lurasidone dosages were 20 mg/day or 60 mg/day. Neither fixed dosage of lurasidone showed a statistically significant difference from placebo on the ABC Irritability subscale. The most common adverse events with lurasidone were vomiting and somnolence.

Olanzapine

The efficacy of olanzapine was evaluated in an 8-week double-blind, placebo-controlled trial that included 11 children and adolescents with pervasive developmental disorders (Hollander *et al.* 2006). Rates of response (CGI-I score [?] 2) were 50% for olanzapine-treated patients and 20% for placebo-treated patients. Olanzapine-treated patients experienced significantly greater weight gain (mean 7.5 lb for olanzapine vs. 1.5 lb for placebo-treated patients).

In a 12-week open-label study of olanzapine (mean dosage = 7.8 mg/day) in eight patients (ages 5-42 years) with DSM-IV autistic disorder or pervasive developmental disorder not otherwise specified, the six patients who completed the trial showed

much or very much global improvement (Potenza *et al.* 1999). Significant improvements were found in hyperactivity, social relatedness, affectual responses, sensory responses, language usage, self-injurious behavior, aggression, irritability, anxiety, and depression. The most significant adverse effects were increased appetite and weight gain in six patients and sedation in three patients.

In a 3-month open study of olanzapine (dosage range = 1.25-20 mg/day) in 25 subjects (ages 6-16 years) with pervasive developmental disorder, significant global improvement was reported. The most common side effect was weight gain (mean = 4.8 kg) (Kemner *et al.* 2002).

Olanzapine was compared with haloperidol in a 6-week open trial of 12 children (ages 4-11 years) with DSM-IV autistic disorder (Malone *et al.* 2001). Both the olanzapine treatment (mean dosage = 7.9 mg/day) and the haloperidol treatment (mean dosage = 1.4 mg/day) reduced symptoms of social withdrawal and stereotypies and improved speech and object relations.

Quetiapine

The effectiveness of quetiapine (dosage range = 100-350 mg/day) was evaluated in a 16-week open-label trial of six pediatric patients with DSM-

IV autistic disorder (Martin *et al.* 1999). No significant behavioral improvements were found from baseline to endpoint.

In a 12-week open-label study of quetiapine in nine adolescents (mean age = 14.6 years) with DSM-IV autistic disorder, only two patients were much or very much improved at study endpoint (Findling *et al.* 2004).

Ziprasidone

The efficacy of ziprasidone was evaluated in a 6-week open-label study of 12 adolescents with autism (Malone *et al.* 2007). Ziprasidone dosages ranged from 20 mg/day to 160 mg/day (mean dosage = 98.3 mg/day). Of the 12 patients, 9 (75%) were considered treatment responders (based on CGI-I scores [?] 2). The mean change in QTc interval from baseline to endpoint was 14.7, which was a statistically significant increase. There was no significant weight change.

The efficacy and safety of ziprasidone in children, adolescents, and young adults with autism were evaluated in an open-label study in which 12 pediatric patients (ages 8-20 years) were treated with ziprasidone (mean daily dosage = 59.23 mg) for at least 6 weeks (McDougle *et al.* 2002). Fifty percent of patients were responders based on a CGI rating of much improved or very much improved. Transient sedation was the most common side effect.

Typical Antipsychotics

Haloperidol

Haloperidol has been the most widely studied typical antipsychotic for the treatment of autism in children and adolescents. In double-blind, placebo-controlled studies, haloperidol has been shown to be significantly superior to placebo in reducing maladaptive behaviors and facilitating learning on discrimination tasks (Campbell *et al.* 1982); increasing retention of discrimination learning and decreasing maladaptive behaviors in the classroom (Anderson *et al.* 1984); decreasing occurrence of stereotypies and increasing orienting reactions of children (Cohen *et al.* 1980); and decreasing hyperactivity, temper tantrums, withdrawal, and stereotypies and increasing relatedness (Anderson *et al.* 1989). Optimal dosages of haloperidol in these studies ranged from 0.25 to 4 mg/day. The most common side effects were sedation, increased irritability, and acute dystonic reactions. Weight gain was modest (0.2 kg) in autistic children who received haloperidol 0.25-3.5 mg/day for a 6-month period (Silva *et al.* 1993).

The long-term efficacy of haloperidol was assessed in 48 children (ages 2-8 years) with autism who received haloperidol for 6 months (Perry *et al.* 1989). Haloperidol remained effective throughout the 6-month treatment period, and it was equally effective whether it was given continuously or on a discontinuous schedule consisting of 5 days on haloperidol and 2 days on placebo. Children who had symptoms of irritability, angry and labile affect, and uncooperativeness were the best responders to haloperidol.

Serotonin Reuptake Inhibitors

Information about dosages, monitoring, and adverse effects of serotonin reuptake inhibitors is provided in the appendix to this chapter.

Fluoxetine

Controlled trials of fluoxetine for treatment of repetitive behaviors have yielded mixed results.

The efficacy of liquid fluoxetine in treating repetitive behaviors in autism was assessed in 45 children and adolescents with ASD. Subjects were randomly assigned to two 8-week acute phases in a double-blind crossover study (Hollander *et al.* 2005). Low-dosage liquid fluoxetine (mean dosage = 9.9 mg/day) was superior to placebo in reducing repetitive behaviors.

The efficacy of fluoxetine in treating obsessive-compulsive symptoms in 146 children and adolescents (ages 7.5-18 years) with ASD was assessed in a 16-week randomized double-blind, placebo-controlled trial (Reddihough *et al.* 2019). The fluoxetine-treated group had significantly lower scores for obsessive compulsive behaviors at 6 weeks than the placebo group.

In a 14-week RCT, fluoxetine was not shown to be superior to placebo for the treatment of repetitive behaviors in 158 youths (ages 5-17 years) with ASD (Herscu *et al.* 2020).

Fluvoxamine

A double-blind, placebo-controlled study investigating fluvoxamine treatment (mean dosage = 106.9 mg/day) in 34 children and adolescents with DSM-IV autistic disorder did not find significant clinical improvement with fluvoxamine (McDougle *et al.* 2000).

Sertraline

The efficacy of sertraline to improve expressive language development was evaluated in a 6-month double-blind placebo-controlled trial of 58 children (ages 24-72 months) (Potter *et al.* 2019). There was no significant difference between sertraline and placebo on change in expressive language scores from baseline to endpoint.

Citalopram

The efficacy of citalopram was evaluated for treatment of repetitive behavior in children with ASD (King *et al.* 2009). One hundred forty-nine children and adolescents with ASD were randomly assigned to receive citalopram or placebo in a 12-week controlled trial. The mean dosage of citalopram at endpoint was 16.5 mg/day. There was no significant difference in rates of response (CGI-I score [?] 2) between citalopram-treated patients (39.2%) and placebo-treated patients (34.2%). No difference was found in reduction in CY-BOCS scores between the citalopram group and the placebo group. Adverse events that were significantly more common in the citalopram group were increased energy level, impulsiveness, hyperactivity, stereotypy, decreased concentration, diarrhea, insomnia, and dry skin or pruritus.

Escitalopram

In a 10-week open-label study, 28 children and adolescents (ages 6-17 years) with pervasive developmental disorder received escitalopram. There was significant improvement in irritability and clinical global functioning. Twenty-five percent of youths responded at escitalopram daily dosages less than 10 mg, and 36% of youths responded at dosages greater than or equal to 10 mg (Owley *et al.* 2005).

Clomipramine

Controlled trials with clomipramine in the treatment of ASD have yielded mixed results. Clomipramine and haloperidol were compared in a placebo-controlled crossover study for 7 weeks with active treatment (Remington *et al.* 2001). Thirty-six patients (ages 10-36 years) with DSM-IV autistic disorder were randomly assigned to clomipramine (mean dosage = 128.4 mg/day; range = 100-150 mg/day), haloperidol (mean dosage = 1.3 mg/day; range = 1-1.5 mg/day), or placebo. A significant advantage for haloperidol was found on global measures of autism symptom severity and on specific measures of irritability and hyperactivity. Clomipramine was comparable to haloperidol only among patients who were able to complete a full therapeutic trial. However, significantly fewer patients receiving clomipramine versus haloperidol were able to complete the trial (37.5% vs. 69.7%, respectively) for reasons related to inefficacy, side effects, or behavioral problems.

Other Antidepressants

Mirtazapine

In an open-label study of mirtazapine (dosage range = 7.5-45 mg/day; mean = 30.3 mg/day) in 26 patients (ages 3-23 years) with pervasive developmental disorders, 9 patients (34.6%) were judged much or very much improved in symptoms of aggression, self-injury, irritability, hyperactivity, anxiety, depression, and insomnia (Posey *et al.* 2001). Mirtazapine did not improve symptoms of social or communication impairment. Common side effects included irritability, increased appetite, and transient sedation.

Venlafaxine

The effectiveness of venlafaxine was assessed in an open retrospective study of 10 patients (ages 3-21 years) with pervasive developmental disorders (Hollander *et al.* 2000). Six of the 10 patients who received venlafaxine (mean dosage = 24.4 mg/day; range = 6.25-50 mg/day) over an average of 5 months were much or very much improved. Improvements were observed in repetitive behaviors, restricted interests, social deficits, communication and language function, inattention, and hyperactivity. Side effects of venlafaxine included behavioral activation, nausea, inattention, and polyuria.

Reboxetine

Eleven adolescents with ASD with depressive and ADHD symptoms were treated with reboxetine (maximum dosage 4 mg/day) in a 12-week open-label trial (Golubchik *et al.* 2013). Significant but modest decreases in depressive and ADHD symptoms were found with reboxetine treatment. Irritability and insomnia were the most commonly reported adverse events.

Mood Stabilizers

Information about dosages, monitoring, and adverse effects of mood stabilizers is provided in the appendix to this chapter.

Lamotrigine

Twenty-eight children (ages 3-11 years) with DSM-IV autistic disorder participated in a double-blind, placebo-controlled study of lamotrigine (mean maintenance dosage = 5 mg/kg/day) for a 12-week study period (Belsito *et al.* 2001). There were no significant differences between the lamotrigine and placebo groups on severity of behavioral symptoms at endpoint. Insomnia and hyperactivity were the most frequently reported side effects. No children in the study were withdrawn because of rash.

Valproate

Three double-blind, placebo-controlled trials have been conducted to assess the efficacy of valproate in the treatment of ASD. In one 8-week trial in 13 children, divalproex was superior to placebo in improvement of repetitive behaviors (Hollander *et al.* 2006). In another 8-week trial that included 27 youths with ASD, divalproex significantly reduced symptoms of irritability compared with placebo (Hollander *et al.* 2010). However, valproate was not superior to placebo in reduction of aggression and irritability for 30 youths with pervasive developmental disorders who participated in an 8-week trial (Hellings *et al.* 2005).

Oxcarbazepine

In a retrospective case series of 30 youths (ages 5-21 years) with ASD, 14 patients (47%) who were treated with oxcarbazepine (mean final dosage = 1,360 mg/day) attained CGI-I scores of 2 or lower on ratings of irritability and agitation symptoms (Douglas *et al.* 2013).

Levetiracetam

A 10-week double-blind, placebo-controlled trial was conducted to assess the efficacy of levetiracetam in the treatment of 20 children with autism (Wasserman *et al.* 2006). The mean maximum dosage of levetiracetam was 862.5 mg/day. There were no significant

differences between levetiracetam and placebo on measures of global improvement of autism, aggression and affective instability, and impulsivity and hyperactivity.

Other Agents

Lithium

In a retrospective chart review of 30 children with ASD who were treated with lithium (mean blood level 0.70 mEq/L), 13 youths (43%) were rated as improved on the CGI-I (Siegel *et al.* 2014). Vomiting, tremor, fatigue, irritability, and enuresis were the most common adverse effects.

Clonidine

A double-blind, placebo-controlled crossover study of transdermal clonidine (0.005 mg/kg/day or placebo delivered via a weekly transdermal patch) in nine patients (ages 5-33 years) with DSM-III-R autistic disorder was conducted for a total active period of 8 weeks (Fankhauser *et al.* 1992). Significantly greater improvement with clonidine, compared with placebo, was found on measures of social relationship, affectual responses, and sensory responses. In a double-blind, placebo-controlled crossover trial of clonidine in eight children with autistic disorder, clonidine was found to be modestly effective in reducing irritability and hyperactivity (Jaselskis *et al.* 1992).

Guanfacine Extended Release

The efficacy of guanfacine ER was assessed in an 8-week randomized, placebo-controlled trial in 62 children with ASD (Scahill *et al.* 2015). The group randomly assigned to guanfacine ER (modal dosage at week 8: 3 mg/day) showed significantly greater decline (43.6%) in scores on the ABC Hyperactivity subscale compared with the placebo group (13.2%). The most common adverse events were drowsiness, fatigue, and decreased appetite.

In a later report involving the same cohort of patients with ASD, guanfacine ER was noted to be superior to placebo in reducing oppositional and repetitive behaviors (Politte *et al.* 2018) at the end of the 8-week trial.

Methylphenidate

A meta-analysis of four methylphenidate trials for treatment of ADHD symptoms in children with pervasive developmental disorders showed an effect size of 0.67 (Reichow *et al.* 2013). The most common adverse events were decreased appetite, insomnia, depressive symptoms, irritability, and social withdrawal.

An extended-release methylphenidate formulation has also been shown to reduce hyperactive and impulsive behavior in children with ASD and

ADHD symptoms (Pearson *et al.* 2013). In 24 children with ASD and symptoms of inattention and hyperactivity, extended-release methylphenidate at low, medium, and high dosages was shown to produce greater improvement than placebo in cognitive task performance (Pearson *et al.* 2020).

Atomoxetine

Atomoxetine as a treatment for symptoms of ADHD in children and adolescents with ASD was examined in a double-blind, placebo-controlled 8-week trial that included 97 youths (Harfterkamp *et al.* 2012). The atomoxetine dosage was 1.2 mg/kg/day. There

was a statistically significant difference between atomoxetine and placebo on change from baseline to endpoint ADHD Rating Scale-IV scores. Adverse effects of nausea, decrease in appetite, fatigue, and early morning awakening were more common in the atomoxetine group than in the placebo group. In a subsequent analysis, atomoxetine did not improve social functioning, but there was some improvement in stereotyped behaviors, inappropriate speech, and fear of change (Harfterkamp *et al.* 2014).

In a placebo-controlled crossover trial that included 16 youths with ASD and ADHD symptoms, atomoxetine was superior to placebo in reduction of hyperactivity and impulsivity symptoms as measured on the ABC (Arnold *et al.* 2006).

Long-term efficacy and tolerability of atomoxetine were assessed in a 20-week follow-up of an 8-week controlled trial in 88 youths with ASD and ADHD symptoms (Harfterkamp *et al.* 2013). Continued treatment with atomoxetine resulted in further improvement of ADHD symptoms. Adverse events, particularly nausea and fatigue, diminished over time with continued treatment.

Atomoxetine, PT, and their combination were assessed in a 10-week randomized placebo-controlled trial in 128 children (ages 5-14 years) with ASD and ADHD symptoms. Atomoxetine--both alone and with PT--

resulted in significant improvement in ADHD symptoms (Handen *et al.* 2015), and no effects on sleep quality were found (Hollway *et al.* 2018). A 24-week extension study showed that atomoxetine responders maintained their response (Smith *et al.* 2016), and a majority maintained improvement at 1.5-year follow-up (Arnold *et al.* 2018).

Bumetanide

The efficacy of bumetanide for the treatment of 60 children with ASD was evaluated in a 3-month double-blind, placebo-controlled trial (Lemonnier *et al.* 2012). The bumetanide dosage was 1 mg/day. Bumetanide was significantly superior to placebo in reduction of symptoms on the primary outcome measure, the Childhood Autism Rating Scale. Occasional mild hypokalemia was the most common adverse event.

Intranasal Oxytocin

Intranasal oxytocin has been examined as a treatment for ASD in controlled trials, with mixed results. Oxytocin nasal spray (18 or 24 IU) or placebo was administered to 16 youths with ASD in a double-blind, placebo-controlled crossover design (Guastella *et al.* 2010). Compared with placebo, oxytocin significantly improved emotion recognition.

In a double-blind, placebo-controlled trial, 36 male youths with ASD received 24 or 12 IU of oxytocin or placebo over a 4-day period (Dadds *et al.* 2014). There were no significant differences between intranasal oxytocin and placebo on measures of social interaction skills, repetitive behaviors, or emotion recognition.

Intranasal oxytocin has been evaluated for the treatment of social deficits in a double-blind, placebo-controlled trial in 50 adolescents with ASD (Guastella *et al.* 2015). There was no significant difference between oxytocin and placebo on the outcome of social responsiveness.

Arbaclofen

The efficacy of arbaclofen was assessed in a 12-week double-blind, placebo-controlled trial that included 150 children, adolescents, and young adults (Delahunty *et al.* 2013).

Arbaclofen was titrated to a maximum of 10 mg three times daily for youths ages 5-11 years and 15 mg three times daily for youths ages 12-21 years. There was no significant difference between arbaclofen and placebo in reducing lethargy or social withdrawal.

Omega-3 Fatty Acids

Omega-3 fatty acids have been evaluated in double-blind, placebo-controlled trials for the treatment of hyperactivity for children with ASD and have shown mixed results. No statistically significant difference between omega-3 fatty acids and placebo has been found on hyperactivity measures in some studies (Bent *et al.* 2011, 2014), although one study reported an advantage of omega-3 fatty acids compared with placebo for hyperactivity and stereotypies (Amminger *et al.* 2007). In a double-blind, placebo-controlled trial, omega-3 plus vitamin D was shown to reduce irritability in children with ASD (Mazahery *et al.* 2019).

Folinic Acid

Folinic acid (2 mg/kg/day) was evaluated as a treatment for language impairment in 48 children (mean age 7 years) with ASD in a 12-week double-blind, placebo-controlled trial (Frye *et al.* 2018). Improvement in verbal communication was significantly greater in the folinic acid group than in the placebo group.

Memantine

Memantine as an adjunctive treatment to risperidone for ASD was assessed in a 10-week double-blind, placebo-controlled trial in 40 children (Ghaleiha *et al.* 2013a). The memantine dosage was titrated to 20 mg/day, and the risperidone dosage to 3 mg/day. Compared with the placebo group, the group that received adjunctive memantine had a significantly greater reduction in the Irritability score on the ABC-Community version. There was no significant difference in adverse effects between the groups.

Amantadine

Amantadine as adjunctive treatment to risperidone for treatment of 40 children with ASD was evaluated in a 10-week double-blind, placebo-controlled trial (Mohammadi *et al.* 2013). Amantadine was titrated to 100-150 mg/day, and risperidone was titrated to 1-2 mg/day. Compared with the placebo group, the adjunctive amantadine group had a significantly greater reduction in Hyperactivity and Irritability scores on the ABC-Community version. There were no significant adverse effects.

Riluzole

The efficacy of riluzole as adjunctive treatment to risperidone was assessed in a 10-week double-blind, placebo-controlled trial for 40 children with ASD (Ghaleiha *et al.* 2013b). Riluzole was titrated to 50-100 mg/day, and risperidone was titrated to 2-3 mg/day. Significantly greater improvement in irritability, as assessed by the ABC-Community version, was found for the adjunctive riluzole group compared with the placebo group. Increased appetite and weight gain were more common in the riluzole group than the placebo group.

Buspirone

Buspirone as adjunctive treatment to risperidone was evaluated in an 8-week double-blind, placebo-controlled trial for 40 youths with autism (Ghanizadeh and Ayoobzadehshirazi 2015). The mean dosage of buspirone was 6.7 mg/day. Compared with the placebo group, the adjunctive buspirone group showed a significantly greater reduction in scores on the Irritability subscale of the ABC-Community version. The most common adverse events in the buspirone group were increased appetite, drowsiness, and fatigue.

In a 24-week RCT in children ages 2-6 years with ASD, low-dosage buspirone (2.5 mg bid) produced significantly greater improvement in restricted and repetitive behaviors compared with placebo (Chugani *et al.* 2016).

Celecoxib

Adjunctive treatment with celecoxib and risperidone was evaluated in a 10-week double-blind, placebo-controlled trial that included 40 children with autism (Asadabadi *et al.* 2013). Celecoxib was titrated to 300 mg/day and risperidone to 3 mg/day. Adjunctive celecoxib was superior to placebo in reducing irritability, social withdrawal, and stereotypy as measured on the ABC-Community version.

Pentoxifylline

The efficacy of adjunctive pentoxifylline with risperidone was assessed in a 10-week double-blind, placebo-controlled trial that included 40 children with a DSM-IV-TR (American Psychiatric Association 2000) diagnosis of autistic disorder (Akhondzadeh *et al.* 2010). Pentoxifylline was titrated to 600 mg/day, and risperidone was titrated to 3 mg/day. Adjunctive pentoxifylline was superior to placebo in reducing scores on the ABC-Community version subscales for irritability, lethargy and social withdrawal, stereotypic behavior, hyperactivity and noncompliance, and inappropriate speech. There was no significant difference between the groups in adverse events.

N-Acetylcysteine

A meta-analysis of five RCTs of NAC with sample sizes ranging from 29 to 98 children with ASD showed that after 8-12 weeks, NAC supplementation improved symptoms of hyperactivity and irritability on the ABC total score (Lee *et al.* 2021). The most common adverse events with NAC supplementation were gastrointestinal symptoms (vomiting, constipation), increased appetite, and upper respiratory infection.

Meta-Analyses: Pharmacological Treatment

With regard to irritability as a feature of ASD, there has been a systematic review and network meta-analysis of the effects of atypical antipsychotics including risperidone, aripiprazole, and lurasidone (Fallah *et al.* 2019). Eight double-blind, placebo-controlled trials with a total of 878 participants were included. Both risperidone and aripiprazole significantly reduced ABC Irritability scores compared with placebo. Risperidone and aripiprazole had similar efficacy.

With regard to restricted and repetitive behaviors as a core symptom of ASD, two recent meta-analyses have examined the effects of pharmacological treatments. A meta-analysis that included 552 participants with ASD in nine RCTs found that none of the medications (fluvoxamine, risperidone, fluoxetine, citalopram, oxytocin, NAC, buspirone) significantly differed from placebo in their effects on restricted and repetitive behavior outcomes (Y. Yu *et al.* 2020).

Another meta-analysis on the pharmacological treatment of restricted and repetitive behaviors in autism included 64 randomized placebo-controlled trials including 3,499 participants with ASD (Zhou *et al.* 2021). Antipsychotics significantly improved restricted and repetitive behaviors compared with placebo, although the effect size was small. Larger significant positive effects on restricted and repetitive behaviors were shown in individual studies of fluvoxamine, buspirone, bumetanide, divalproex, guanfacine, and folinic acid, but these studies have not been replicated. Other pharmacological treatments including oxytocin, omega-3 fatty acids, SSRIs, and methylphenidate did not significantly reduce restricted and repetitive behavior compared with placebo.

Clinical Recommendations for Autism Spectrum Disorder

Although there is no evidence that pharmacotherapy is effective in treating the core social and communication deficits in ASD, medications have been shown to be useful in treating associated symptoms, such as hyperactivity, inattention, stereotypies, self-injurious behavior, tantrums, aggression, mood lability, and anxiety. Antipsychotics may decrease withdrawal, stereotypies, and aggression and may facilitate learning. Most available data support the use of risperidone or aripiprazole for treating irritability, aggression, self-injurious behavior, temper tantrums, and mood lability associated with ASD in children and adolescents. Serotonin reuptake inhibitors and other antidepressants have been shown to reduce compulsions, anxiety, and depression in children with ASD. Other agents that may be beneficial in treating associated symptoms are a_2 agonists, stimulants, mood stabilizers, and norepinephrine reuptake inhibitors (Volkmar *et al.* 2014).

Limited data are available on the long-term use of pharmacotherapy in children with ASD. After receiving an intermediate-length (4-to 6-month) course of treatment with risperidone, children withdrawn from the medication through placebo substitution had high relapse rates (Research Units on Pediatric Psychopharmacology Autism Network 2005; Troost *et al.* 2005). Therefore, clinicians must weigh the risk-benefit ratio of maintenance medication treatment in this population and carefully monitor children for side effects.

Conclusion

The evidence base for medication treatment of child and adolescent psychiatric disorders continues to grow. More clinical trials are needed to assess the efficacy and safety of medication augmentation strategies, as well as the optimal duration of treatment. The goal of appropriate psychopharmacological management is not only to reduce acute symptoms but also to prevent long-term impairment in children and adolescents.

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APPENDIX

Psychotropic Medications Commonly Prescribed for Children and Adolescents

This appendix describes common classes of psychotropic medications used to treat children and adolescents. Dosing information, monitoring schedules, and common side effects are presented for each medication class.

Antidepressants

Dosage and Monitoring

The starting dosages and target dosages of antidepressants for children and adolescents are listed in Table 60-1. Premedication laboratory testing should include complete blood count, blood chemistries, and liver function tests. Blood pressure should be monitored during dosage titration with venlafaxine. The U.S. Food and Drug Administration (2007) issued the following black box warning, which applies to all antidepressants:

TABLE 60-1. Clinical use of antidepressants in children and adolescents

Medication	Typical starting dosage (mg) Child	Typical starting dosage (mg) Adolescent	Target dosage (mg/day)
Selective serotonin reuptake inhibitors			
Citalopram	5-10	10	20-40
Escitalopram	5	10	10-20
Fluoxetine	5-10	10	20-40
Paroxetine[a]	5-10	10	20-40
Sertraline	25	50	100-200
Mirtazapine	15	15	30-45
Venlafaxine[b]	37.5	37.5	150-225
Bupropion[a]	37.5 bid	37.5 bid	100-300
Duloxetine	30	30	60-120
Desvenlafaxine	25	25	25-25

[a] Immediate-release hydrochloride salt.

[b] Extended-release hydrochloride salt capsule.

> Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Name of Antidepressant] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24 years; there was a reduction in risk with antidepressants compared with placebo in adults ages 65 years and older. Depression and certain other psychiatric disorders are themselves

> associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

Side Effects

Common side effects of SSRIs are headache, nausea, abdominal pain, dry mouth, insomnia, and somnolence (Emslie *et al.* 2002; Keller *et al.* 2001; Wagner *et al.* 2003a, 2004b, 2006a). Potential serious adverse events include serotonin syndrome, EPS (tics, myoclonus), amotivational syndrome, and increased bleeding (Hammerness *et al.* 2006). A major advantage of SSRIs is their safety in overdose (Barbey and Roose 1998).

Common side effects of mirtazapine are somnolence, increased appetite, weight gain, dizziness, dry mouth, and constipation (Green 2001).

Common side effects of venlafaxine include anorexia, abdominal pain, insomnia, somnolence, dizziness, dry mouth, increased sweating and nervousness, and elevated blood pressure with dosage increase (Emslie *et al.* 2007; Green 2001).

Common side effects of bupropion are headache, nausea, rash, irritability, drowsiness, fatigue, and anorexia (Barrickman *et al.* 1995; Conners *et al.* 1996; Daviss *et al.* 2001). Bupropion is contraindicated in children with seizure disorders, because it may lower the seizure threshold.

Common side effects of duloxetine are nausea, vomiting, nasopharyngitis, abdominal pain, headache, and somnolence (Atkinson *et al.* 2014; Emslie *et al.* 2014).

Common side effects of desvenlafaxine are headache, abdominal pain, nausea, and dizziness (Atkinson *et al.* 2014; Weihs *et al.* 2018).

In a network meta-analysis of antidepressants for MDD in children and adolescents, fluoxetine was more tolerable than duloxetine. Venlafaxine-and duloxetine-treated youths had more discontinuations due to adverse events than those given placebo (Cipriani *et al.* 2016).

In a large-scale systematic meta-review that included six antidepressants (sertraline, escitalopram, paroxetine, fluoxetine, venlafaxine, and vilazodone), fluoxetine and escitalopram had more favorable safety profiles than other antidepressants in children and adolescents (Solmi *et al.* 2020).

Atypical Antipsychotics

Dosage and Monitoring

The usual starting dosages and target dosages of atypical antipsychotics are listed in Table 60-2. Premedication laboratory testing should include complete blood count, blood chemistries, and liver function tests. In addition, the recommendations of the American Diabetes Association *et al.* (2004) should be followed. Baseline measures should be obtained for BMI, waist circumference, blood pressure, and fasting glucose and lipid panels. BMI should be followed monthly for 3 months and then measured quarterly. Blood pressure, fasting glucose, and lipid panels should be followed up at 3 months and then yearly. Monitoring should also be done for EPS.

TABLE 60-2. Clinical use of atypical antipsychotics in children and adolescents

Medication	Typical starting dosage (mg)	Target dosage (mg/day)
Clozapine*	12.5-25 bid	200-500
Olanzapine	2.5 bid	10-20
Quetiapine IR	25-50 bid	400-800
Quetiapine XR	50 bid	400-800
Risperidone	0.25 bid	1-3
Ziprasidone*	20 bid	80-120

Note. ER = extended release; IR = immediate release; XR = extended release.

*Off-label use (Safety and effectiveness in pediatric patients have not been established).

Source. Adapted from Kowatch and DelBello 2006.

Medication	Typical starting dosage (mg)	Target dosage (mg/day)
Aripiprazole	2.0-5.0 hs	10-30
Asenapine	2.5 sublingually bid	2.5-10 sublingually bid
Paliperidone ER		
Weight < 51 kg	3	3-6
Weight [?] 51 kg	3	3-12

Note. ER = extended release; IR = immediate release; XR = extended release.
*Off-label use (Safety and effectiveness in pediatric patients have not been established).
Source. Adapted from Kowatch and DelBello 2006.

Side Effects

Side effects of atypical antipsychotics include weight gain, dyslipidemia, insulin resistance and diabetes, hyperprolactinemia, EPS and akathisia, QTc prolongation, sedation, liver toxicity, neutropenia, and neuroleptic malignant syndrome. Clozapine has also been associated with seizures, agranulocytosis, and myocarditis (Correll *et al.* 2006).

In a large-scale systematic meta-review that included eight antipsychotics (risperidone, quetiapine, aripiprazole, lurasidone, paliperidone, ziprasidone, olanzapine, and asenapine), lurasidone had a more favorable safety profile than the other antipsychotics in children and adolescents (Solmi *et al.* 2020). Of the antipsychotics, the most safety concerns were with olanzapine for children and adolescents.

In a systematic review and meta-analysis of antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) in children and adolescents with schizophrenia spectrum disorders, weight gain was associated primarily with olanzapine, EPS and akathisia with molindone, and prolactin increase with risperidone, paliperidone, and olanzapine (Pagsberg *et al.* 2017b).

Mood Stabilizers

Dosage and Monitoring

The starting dosages, target dosages, and therapeutic serum levels of mood stabilizers are listed in Table 60-3. Premedication laboratory testing in general should include complete blood count, liver function tests, and a pregnancy test (for female patients).

TABLE 60-3. Clinical use of mood stabilizers in children and adolescents

Medication	Typical starting dosage (mg)	Target dosage	Therapeutic serum level
Carbamazepine	7 mg/kg/day	Based on response and serum level	8-11 mg/L
Lamotrigine	12.5 mg/day	Based on response	N/A
Lithium	25 mg/kg/day[b]	30 mg/kg/day[b]	0.8-1.2 mEq/L
Oxcarbazepine	150 mg bid	20-29 kg: 900 mg/day[a] 30-39 kg: 1,200 mg/day[a] > 39 kg: 1,800 mg/day[a]	N/A
Topiramate	25 mg/day	100-400 mg/day	N/A
Valproic acid, divalproex	20 mg/kg/day[a]	20 mg/kg/day[b]	90-120 mg/mL

Note. N/A = not applicable.

[a] Divided into 2 daily doses.

[b] Divided into 2-3 daily doses.

Source. Adapted from Kowatch and DelBello 2006.

For lithium, baseline thyroid function tests, electrolytes, urinalysis, blood urea nitrogen, creatinine, and serum calcium should also be obtained. Lithium levels, renal function, thyroid function, and urinalysis should be monitored every 3-6 months.

For patients taking divalproex, drug serum levels, complete blood count, and liver function tests should be monitored every 3-6 months. Because of concerns about a possible relationship between divalproex and polycystic ovary syndrome (PCOS; Rasgon 2004), female adolescents taking divalproex should be monitored for signs of PCOS, including menstrual abnormalities, weight gain, acne, and hirsutism (DelBello and Kowatch 2006; McClellan *et al.* 2007). Parents and their female adolescents should be apprised about this possible association before initiating medication.

For oxcarbazepine, children should be monitored for hyponatremia.

Side Effects

Common side effects of lithium in children and adolescents include hypothyroidism, nausea, polyuria, polydipsia, acne, tremor, and weight gain (DelBello and Kowatch 2006).

Common side effects of divalproex in children and adolescents include weight gain, nausea, sedation, and tremor (DelBello and Kowatch 2006). Concerns have been raised about a possible association between divalproex and PCOS (Rasgon 2004). Other potential adverse effects of concern are hepatic failure, pancreatitis, thrombocytopenia, behavioral deterioration, and hair loss (Davanzo and McCracken 2000; Green 2001).

Side effects of topiramate include decreased appetite, weight loss, nausea, diarrhea, paresthesias, somnolence, and word-finding difficulties (DelBello and Kowatch 2006; DelBello *et al.* 2005).

Side effects of oxcarbazepine in children include dizziness, nausea, somnolence, diplopia, fatigue, and rash (Wagner *et al.* 2006b). Hyponatremia is also a side effect of oxcarbazepine.

Common side effects of lamotrigine in children include ataxia, nausea, vomiting, and constipation. Of particular concern, the incidence of serious rash, including Stevens-Johnson syndrome, in pediatric populations is reported to be 1%. This high incidence of serious rash may be attributable to prior use of high dosages of lamotrigine with concomitant divalproex (Messenheimer 1998). The current dosing guidelines may reduce this rash incidence in pediatric patients.

A large-scale systematic meta-review of the safety of antidepressants, antipsychotics, anti-ADHD medications, and mood stabilizers in children and adolescents included two mood stabilizers (valproate and lithium). Lithium showed a more favorable safety profile than valproate in children and adolescents (Solmi *et al.* 2020).

Atomoxetine

Dosage and Monitoring

Atomoxetine can be taken in the late afternoon or evening, whereas stimulants generally cannot; atomoxetine may have less pronounced effects on appetite and sleep than stimulants, although it may produce more nausea or sedation. Gastrointestinal distress can be minimized by taking the medication after a meal. In children and young adolescents, atomoxetine is initiated at a dosage of 0.3 mg/kg/day and titrated over 1-3 weeks to a maximum dosage of 1.2-1.8 mg/kg/day (Kratochvil *et al.* 2003). In adults or adult-sized adolescents, atomoxetine should be started at 40 mg/day and titrated to 80-100 mg/day over 1-3 weeks, if needed (Kratochvil *et al.* 2003). Atomoxetine's labeling recommends either once-daily or twice-daily dosing, although atomoxetine's elimination half-life of 5 hours (as well as clinical experience) suggests that twice-daily dosing (early morning and early evening) is more effective and less likely to cause side effects. Michelson *et al.* (2002) showed that although atomoxetine

was superior to placebo at week 1 of the trial, its greatest effects were observed at week 6, suggesting that patients should be maintained at the full therapeutic dosage for at least several weeks for the drug to reach its full effects.

Side Effects

Side effects that occurred at higher rates with atomoxetine than with placebo in clinical trials included gastrointestinal distress, sedation, and decreased appetite. These effects can generally be managed by dosage adjustment and often attenuate with time. Since 2005 the label for atomoxetine has carried a black box warning regarding rare cases of suicidal ideation, but a large retrospective cohort study involving more than 250,000 patients showed no increased risk of suicidal ideation in those treated with atomoxetine relative to those treated with stimulants (Linden *et al.* 2016).

Alpha-2 Adrenergic Receptor Agonists

Dosage and Monitoring

The initial starting and target dosages for both clonidine and guanfacine are shown in Table 60-4.

TABLE 60-4. Titrations of alpha-2 agonists

	Typical starting dosage (mg)		
Medication	**Child**	**Adolescent**	**Target dosage (mg/day)**
Guanfacine IR	0.5 hs	1 hs	1-4
Guanfacine XR	1	1	1-4
Clonidine IR	0.05	0.1	0.2-0.4 (divided into 3 or 4 daily doses)
Clonidine XR	0.1	0.2	0.1-0.4 (divided into 2 daily doses or a higher dose at bedtime)

Note. IR = immediate release; XR = extended release.

Side Effects

Pooling of all adverse events reported in clinical trials of a_2 agonists showed that rates of fatigue, sedation, and somnolence were significantly higher with these medications than with placebo (Hirota *et al.* 2014). Sedation tends be much more common with clonidine than with guanfacine. Data from five studies of a_2 agonists showed no significant differences in blood pressure with guanfacine, but clonidine immediate release was associated with a mean drop of 5.2 mm Hg in systolic blood pressure. a_2 Agonists may be associated with an increase in the QTc interval (Hirota *et al.* 2014). In the 1990s, concerns were raised about isolated cases of sudden death, particularly in children taking clonidine in combination with methylphenidate, but these concerns have not persisted, as subsequent studies of a_2 agonists in the treatment of ADHD have not reported any serious cardiovascular adverse effects (Fay and Alpert 2019a, 2019b; Martinez-Raga *et al.* 2013). Therefore, routine electrocardiogram (ECG) monitoring in patients without any cardiac history is not necessary.

Psychostimulants

Dosage and Monitoring

A wide variety of stimulant preparations are available; Table 60-5 describes their use in clinical practice. Each stimulant has a maximum dosage suggested by the FDA-approved package insert, but higher off-label dosages are commonly used with careful monitoring. For safety monitoring, a patient's pulse, blood pressure, weight, and height should be obtained at baseline and at least annually. No laboratory measures or ECG monitoring is required.

TABLE 60-5. Clinical use of psychostimulants in children and adolescents

Medication	Dosage strengths	Typical starting dosage	FDA maximum/day	Off-label maximum/day

Medication	**Dosage strengths**	**Typical starting dosage**	**FDA maximum/day**	**Off-label maximum/day**
Amphetamine preparations				
Adderall	5, 7.5, 10, 12.5, 15, 20, 30 mg	3-5 yr: 2.5 mg qd [?] 6 yr: 5 mg qd-bid	40 mg	[?] 50 kg: 60 mg
Dexedrine	5 mg	3-5 yr: 2.5 mg qd [?] 6 yr: 5 mg qd-bid	40 mg	[?] 50 kg: 60 mg
Dextrostat	5, 10 mg	3-5 yr: 2.5 mg qd [?] 6 yr: 5 mg qd-bid	40 mg	[?] 50 kg: 60 mg
Dexedrine Spansule	5, 10, 15 mg	[?] 6 yr: 5-10 mg qd	40 mg	[?] 50 kg: 60 mg
Adderall XR	5, 10, 15, 20, 25, 30 mg	[?] 6 yr: 10 mg qd	30 mg	[?] 50 kg: 60 mg
Vyvanse	30, 50, 70 mg	30 mg qd	70 mg	100 mg
Adzenys	3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg	6.3 mg	40 mg	ND
Mydayis	12.5, 25, 37.5, 50 mg	2.5-5.0 mg qd	50 mg	ND
Dyanavel	2.5 mg/mL	2.5 mg	20 mg	ND

Medication	Dosage strengths	Typical starting dosage	FDA maximum/day	Off-label maximum/day
Evekeo	5, 10, 15, 20 mg	2.5 mg	ND	ND
Zenzedi	2.5, 5, 7.5, 10, 15, 20 mg	2.5 mg	60 mg	60 mg
Methylphenidate preparations				
Focalin	2.5, 5, 10 mg	2.5 mg bid	20 mg	50 mg
Focalin XR	5, 10, 15, 20 mg	5 mg qam	30 mg	50 mg
Methylin	5, 10, 20 mg	2.5-5.0 mg bid	60 mg	[?] 50 kg: 100 mg
Metadate ER[a]	--[a]			
Methylin ER	10, 20 mg	10 mg qam	60 mg	[?] 50 kg: 100 mg
Ritalin SR[a]	--[a]			
Metadate CD	10, 20, 30, 40, 50, 60 mg	20 mg qam	60 mg	[?] 50 kg: 100 mg
Ritalin LA	10, 20, 30, 40 mg	20 mg qam	60 mg	ND
Concerta	18, 27, 36, 54 mg	18 mg qam	72 mg	108 mg
Daytrana patch	10-, 15-, 20-, 30-mg patches	Begin with 10-mg patch qd, then titrate up by	30 mg	ND

Medication	Dosage strengths	Typical starting dosage	FDA maximum/day	Off-label maximum/day
		patch strength		
Quillivant XR	25 mg/5 mL	2 mL qam	12 mL	ND
QuilliChew ER	20, 30, 40 mg	20 mg	60 mg	ND
Adhansia XR[a]	--[a]			
Aptensio XR	10, 15, 20, 30, 40, 50, 60 mg	10 mg qam	60 mg	ND
Jornay PM	20, 40, 60, 80, 100 mg	20 mg (take in evening between 6:30 and 9:30 P.M.)	100 mg	ND
Cotempla XR	8.6, 17.3, 25.9 mg	8.6-17.3 mg	51.8 mg	ND

Note. CD = controlled delivery (extended release); ER = extended release; LA = long acting (extended release); ND = not determined; SR = sustained release; XR = extended release.

[a] Brand-name product removed from the U.S. market.

Source. PDR Network LLC: PDR Prescribers' Digital Reference (https://www.pdr.net/). Whippany, NJ, ConnectiveRx, n.d. Accessed July 1, 2023. Stevens JR, Wilens TE: "Stimulant Medication in Children and Adolescents," in *Attention-Deficit Hyperactivity Disorder in Adults and Children*. Edited by Adler LA, Spencer TJ, Wilens TE. Cambridge, UK, Cambridge University Press, 2015, pp. 245-258.

Side Effects

Stimulant adverse effects commonly include immediate short-term effects such as insomnia (12.3%), headaches (14.5%), and reduced appetite (28.6%) (Cerrillo-Urbina *et al.* 2018). These are generally self-limited and resolve within a month, but they can make a child so uncomfortable as to result in discontinuation. Emotional side effects are more rare; the issue is confounded by the fact that stimulants often improve the mood lability that is often associated with ADHD. Meta-analyses suggest that overall, methylphenidate reduces mood lability, whereas amphetamine may have a slight tendency to increase it (Pozzi *et al.* 2018). If a child shows a distinct worsening of mood after starting a stimulant, that agent should be discontinued, but this does not preclude a trial of an alternative stimulant.

In one study, stimulants induced very modest increases in blood pressure and pulse, with no differences in the number of adverse cardiac events between participants receiving methylphenidate treatment and those receiving placebo (Dalsgaard *et al.* 2014). A meta-analysis of three studies with 775 adults also found no significant difference in adverse cardiac events between methylphenidate and placebo (E. F. Liang *et al.* 2018), nor was methylphenidate associated with a higher risk of all-cause death, heart attack, or stroke (Liu *et al.* 2019). Routine ECG monitoring of patients who do not have a cardiac disease history is not necessary when treating ADHD with stimulants (Fay and Alpert 2019a, 2019b).

A review of 109 studies concluded that the nonmedical use of prescribed stimulants is a significant public health problem, especially in college students, despite the fact that stimulants may not improve academic performance in individuals without ADHD (Faraone *et al.* 2020). Common methods of diversion include obtaining prescriptions from multiple prescribers or filling prescriptions at multiple pharmacies, and such behaviors were four times more common in the ADHD group than in a comparison group of patients with asthma (Cepeda *et al.* 2014).

The effect of stimulants on growth has been the subject of multiple long-term studies. The most recent meta-analysis (Carucci *et al.* 2020) suggests that long-term use of stimulants is associated with minor impacts on height and weight in children and adolescents with ADHD (pre/post difference for height Z score, SMD = 0.27; weight Z score, SMD = 0.35). Although such an effect could reduce mean height gain by approximately 1.39 cm and weight gain by approximately 1.96 kg for a 10-year-old boy over a 2-year period, the growth effect appears to plateau by late adolescence. Thus, ultimate height and weight effects may be quite small at the individual level and not clinically significant.

Viloxazine

Dosage

In children ages 6-11 years, the recommended starting dosage for viloxazine is 100 mg once daily. Viloxazine may be titrated in increments of 100 mg weekly to the maximum recommended dosage of 400 mg once daily. For adolescents ages 12-17 years, the clinician should start at 200 mg once daily; the dosage may be increased after 1 week, by an increment of 200 mg, to the dosage of 400 mg once daily. The capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce.

Side Effects

In clinical trials, viloxazine was well tolerated; adverse events that occurred at rates significantly greater than those of placebo were somnolence (14%), decreased appetite (7.7%), fatigue (7.2%), headache (6.8%), and upper abdominal pain (4.8%). Severe adverse events were rare and were not different between the placebo and viloxazine groups. There were no clinically meaningful changes in ECG, vital signs, or laboratory measures.

CHAPTER 61

Treatment During Late Life

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Adverse events caused by medication are a significant cause of morbidity and mortality in older adults. In a large study of ambulatory Medicare enrollees, 38% of adverse drug events were serious, life-threatening, or fatal, and 28% were considered preventable (Gurwitz *et al.* 2003). Moreover, psychotropics are among the most common medications associated with preventable adverse drug events in elderly patients in long-term care settings (Davies and O'Mahony 2015).

Pharmacokinetics of Psychotropic Medications in Older Adults

Age-associated pharmacokinetic differences may be due to changes in absorption, distribution, metabolism, or elimination of a drug (Table 61-1). In general, age-associated pharmacokinetic changes result in higher and more variable drug concentrations. Although individuals older than 65 years account for more than one-half of prescription drug expenditures in the United States, they are often excluded from clinical and regulatory trials. The trials that do include older adults rarely include the "oldest old" (i.e., 85+ years), those with multiple comorbidities, or those taking multiple medications, and these omissions raise questions about the generalizability of psychotropic data to the frail elderly. Therefore, specific information on the pharmacokinetics of most psychoactive medications is inadequate, particularly regarding medical comorbidities and potential drug interactions. The limited information that does exist for older subjects is largely derived from traditional pharmacokinetic studies, which usually are not adequate to rule out the possibility of nonlinear kinetics.

TABLE 61-1. Physiological changes in older adults associated with altered pharmacokinetics

Organ system	Change	Pharmacokinetic consequence
Gastrointestinal tract	Decreased intestinal and splanchnic blood flow	Decreased rate of drug absorption
Circulatory	Decreased concentration of plasma albumin and increased a_1-acid glycoprotein	Increased or decreased free concentration of drugs in plasma
Kidney	Decreased glomerular filtration rate	Decreased renal clearance of active metabolites
Muscle	Decreased lean body mass and increased adipose tissue	Altered volume of distribution of lipid-soluble drugs, leading to increased elimination half-life
Liver	Decreased liver size; decreased hepatic blood flow; minimal effects on cytochrome P450 enzyme activity	Decreased hepatic clearance

Absorption

Although absorption of nutrients is often impaired in older persons, the rate and extent of passive drug absorption are not affected by normal aging. However, antacids and high-fiber supplements may significantly diminish the absorption of medications.

Distribution

Because a drug's half-life is directly proportional to its apparent volume of distribution, loss of lean body mass with aging will result in longer half-lives and drug accumulation for most lipid-soluble psychotropics. Conversely, for water-soluble drugs (e.g., lithium and digoxin), volumes of distribution will be diminished in older patients, reducing the margin of safety after acute increases in plasma drug concentration.

Reductions in serum albumin with age and increases in a_1-acid glycoprotein with illness may affect the extent of drug bound to plasma proteins. However, changes in plasma protein binding are of clinical significance only when therapeutic drug monitoring is used to adjust dosing, because total drug concentrations (free + protein bound) are usually reported (Benet and Hoener 2002). Therefore, total drug levels may be interpreted as too low if a drug's free fraction is increased by diminished plasma proteins or drug displacement.

Metabolism

Available evidence suggests that there is no uniform age-associated decline in liver metabolism by cytochrome P450 (CYP) enzymes (Schmucker 2001). Nonetheless, reductions in hepatic mass and blood flow with aging place greater emphasis on interindividual differences in drug metabolic capacity that may be due to genetics or medication interactions.

In recent years, pharmacogenetic testing has become increasingly available for clinicians, and such instruments may be used to genetically guide treatment with psychotropic medications. Among the many pharmacogenetic tests that have been proposed, genetic variation in

CYP2D6 enzymes can most clearly affect pharmacokinetic parameters but does not obviously affect antidepressant treatment response. According to guidelines put forth by the International Society of Psychiatric Genetics, there is inconclusive evidence to support widespread use of pharmacogenomic tests other than *HLA-A* and *HLA-B* prior to the use of carbamazepine and oxcarbazepine. However, genetic information for *CYP2D6* and *CYP2C19* would likely be most beneficial for persons who have experienced an inadequate response or an adverse reaction to a previous antidepressant or antipsychotic trial (International Society of Psychiatric Genetics 2019). Therefore, the Clinical Pharmacogenetics Implementation Consortium recommends dosing based on *CYP2D6* and *CYP2C19* genotypes for tricyclic antidepressant (TCA) and selective serotonin reuptake inhibitor (SSRI) medications in adults (Hicks *et al.* 2017). However, further studies are needed to validate evidence for these recommendations in older adults.

CYP2D6 and CYP2C19 are the enzymes responsible for metabolizing 50%-60% of all antidepressants as well as many antipsychotics (Marshe *et al.* 2020). Frequency differences for known *CYP2D6* polymorphisms vary across ethnic and racial groups and are more common in white individuals (5%-10% of whites are poor metabolizers of CYP2D6) (de Leon *et al.* 2006). A few studies have examined the effect of CYP2D6 metabolization on drug plasma levels and metabolite concentration levels in older adults (Marshe *et al.* 2020). For example, plasma levels of venlafaxine have been found to be associated with genetically determined CYP2D6 enzyme activity in older adults with depression (Whyte *et al.* 2006). However, there is limited evidence that CYPD26 metabolism alters the dosing of antidepressant medications (Bijl *et al.* 2008) and no evidence that enzymatic activity affects response to antidepressant treatment in older adults (Marshe *et al.* 2020).

In parallel, CYP2C19 metabolizes several antidepressants, such as citalopram, escitalopram, and amitriptyline. Poor metabolizers of CYP2C19 are common and account for up 25% of East Asians (de Leon *et al.* 2006), but there is limited information regarding the pharmacokinetic effects of *CYP2C19* polymorphisms for antidepressants. One analysis found that among CYP2C19 poor metabolizers, adults older than 65 years had a 1.4-fold higher mean escitalopram concentration compared with younger adults

(< 40 years), but this difference did not reach statistical significance (Waade *et al.* 2014).

Drugs metabolized by CYP3A4, such as alprazolam, clonazepam, carbamazepine, and mirtazapine, appear to be cleared less well in elderly patients (Ronfeld *et al.* 1997). However, this may be because metabolism of CYP3A4-metabolized drugs is typically perfusion-limited (i.e., dependent on hepatic blood flow, which can decline with age). CYP3A4 is substantially responsible for the "first-pass," or presystemic, drug disposition, as it makes up 30% of total hepatic CYP and nearly all drug-metabolizing enzyme in the small bowel (Shimada *et al.* 1994). CYP3A4 activity may be inhibited by fluvoxamine, fluoxetine, grapefruit juice, protease inhibitors, macrolide antibiotics, and triazole antifungals. The CYP3A4 enzyme is also potently induced by other drugs, such as carbamazepine, phenytoin, topiramate, modafinil, barbiturates, steroids, and St. John's wort, which may increase the likelihood of therapeutic failure for concurrently prescribed CYP3A4 substrate drugs.

CYP1A2 metabolizes clozapine, olanzapine, and fluvoxamine and contributes to the demethylation of some tertiary TCAs. This enzyme is induced by cigarette smoking, cruciferous vegetables, and charcoal-broiled meat. For example, abrupt cessation of smoking can increase clozapine levels and elevate the risk of toxicity.

Excretion

Age-associated decline in renal clearance may affect excretion of psychotropic drug metabolites and lithium in older patients. The magnitude of this decline varies greatly among the aged, being exacerbated by concomitant conditions (e.g., diabetes and hypertension) and medications (e.g., nonsteroidal anti-inflammatory drugs). Renal clearance of TCA metabolites can be reduced by normal aging, accounting for increased risk of toxicity (Pollock *et al.* 1992). Higher concentrations of bupropion and venlafaxine metabolites also have been observed in older patients and those with renal impairment, with uncertain clinical consequences.

Pharmacodynamics of Psychotropic Medications in Older Adults

Interindividual differences in pharmacodynamics become evident when those with similar plasma drug concentrations experience different effects. In general, older individuals are more sensitive to adverse effects of psychotropics at lower concentrations. Homeostatic mechanisms (e.g., postural control, water balance, orthostatic circulatory responses, and thermoregulation) are frequently less robust in older adults and may interfere with the ability to physiologically adapt to medication.

For this reason, all antidepressants may increase the risk of falls and hip fractures, although recent literature has raised questions about the strength of this association (Brannstrom *et al.* 2019). Similarly, the syndrome of inappropriate antidiuretic hormone secretion has been reported as an age-associated adverse effect of SSRIs (Kirby and Ames 2001). Reductions in dopamine or acetylcholine function with age may increase an individual's sensitivity to antipsychotics and SSRIs as well as to medications with antimuscarinic effects (Graff-Guerrero *et al.* 2015). For example, use of anticholinergic medications is associated with an increased risk for cognitive dysfunction and brain atrophy (Risacher *et al.* 2016), although these agents continue to be widely prescribed in older patients (Grossi *et al.* 2020).

Anticoagulant-antidepressant interactions may be both pharmacokinetic and pharmacodynamic. Fluvoxamine and fluoxetine pose the greatest risk of pharmacokinetic interactions through CYP2C9 inhibition, reducing the clearance of warfarin's active *S*-enantiomer. However, increased bleeding times with SSRIs alone or in combination with anticoagulants or nonsteroidal anti-inflammatory drugs also may be possible as a result of the effect of these medications in depleting platelets of serotonin and attenuating their aggregation (Pollock *et al.* 2000b; Shin *et al.* 2015).

At present, there exists only preliminary evidence that genetic differences may influence pharmacodynamics in older patients. For example, polymorphisms in genes encoding serotonin transporters, norepinephrine transporters, and brain-derived neurotrophic factor have been suggested to contribute to patient variability in antidepressant effects (Marshe *et al.* 2020). Several studies have shown that the homozygous

genotype of the long-long (LL) serotonin transporter promoter genotype is associated with better treatment outcomes with SSRIs in younger and older adults (Fabbri and Serretti 2015; Serretti *et al.* 2006). For example, depressed elderly patients with the LL serotonin transporter promoter genotype were found to have a more rapid initial response to paroxetine (Pollock *et al.* 2000a). However, an analysis of late-life depression in Korea found the opposite result--that is, better responses among carriers of the short (S) allele (Kim *et al.* 2006).

Antidepressants in Older Adults

Late-Life Depression

In cross-sectional surveys, only 3% of community-dwelling adults older than 60 years have symptoms that meet criteria for a current major depressive episode (NIH Consensus Conference 1992), but 15% of older adults have clinically significant depressive symptoms (Rothschild 1996). Such subthreshold symptomatology is important given its deleterious consequences, which include increasing an older adult's risk of disability, increasing mortality in patients with heart disease, and being associated with high rates of completed suicide in individuals older than 65 years. Compounding this public health burden are the facts that late-life depression is highly recurrent, can become chronic (Alexopoulos *et al.* 1996), and is often difficult to treat (Sneed *et al.* 2008).

Late-life neuropsychiatric disorders are increasingly recognized as the products of complex interactions between psychopathology and aging processes affecting brain structure and function. Thus, late-life depression is hypothesized to be a collection of subtypes distinguished from each other by their relationships to distinct aging processes, underlying biomarkers, salient behavioral manifestations, clinical characteristics, and treatment responsivity.

Vascular depression is a proposed subtype of late-life depression that is characterized by vascular lesions in deep white matter tracts that disconnect prefrontal cortical regions from striatal and limbic areas, causing depressive symptoms and executive dysfunction.

A second proposed subtype, *depression with slowing*, is believed to result from the age-dependent increase in inflammation (called "inflammaging"). One such adverse effect of inflammaging concerns dopaminergic functioning, which declines linearly with age and is implicated in the development of psychomotor slowing. Studies have established an association between inflammation-induced dopaminergic dysfunction and the development of depressed mood, anhedonia, and deficient reward processing (Capuron *et al.* 2012; Felger and Miller 2012; Raison *et al.* 2006). Psychomotor slowing (as evidenced by decreased gait speed) may increase stress, impair function, and decrease activity levels and may represent an intermediate step on a pathway to late-life depression. Furthermore, slowed processing speed not only is a negative prognostic factor in antidepressant treatment but also places older individuals on an unhealthy aging trajectory characterized by poor health outcomes (Taylor *et al.* 2006).

Depression related to frailty is a third proposed subtype of late-life depression, because fatigue is a cardinal feature of depression and a core characteristic of the syndrome of frailty (weakness, decreased activity levels, slowed gait speed, and unintentional weight loss) (Bandeen-Roche *et al.* 2006; Fried *et al.* 2001). Given that mitochondria produce most of the body's energy, age-related decline in mitochondrial output constitutes part of the biological basis for the physical and mental fatigue and the pathophysiology of the frailty-associated subtype. Declining mitochondrial output may underlie the cognitive impairment, slowing, and fatigue that are characteristic of late-onset depression. Such qualities may help to explain the heterogeneity of late-onset depression and why its diverse symptoms do not respond as well to antidepressant medication, a treatment that does not target any of these pathologies.

Antidepressant Treatment in Older Patients

Variability in results of randomized controlled trials of antidepressants in late-life depression may result from heterogeneity in the patient population and study design. The standard considerations in study design--namely, randomization, placebo versus comparator control, dosage, duration, and criteria for response and remission--are all important, but specifically the value of placebo-controlled trials versus comparator trials and optimal duration of treatment have been systematically reexamined. Sneed *et al.* (2008) conducted a meta-analysis of all studies published in peer-reviewed journals from 1985 to 2006 that were randomized placebo-controlled or comparator (a comparison of two active conditions) trials of antidepressants for the treatment of late-life depression. The intent of the meta-analysis was to determine whether rates of response to medications in comparator trials are significantly higher than rates of response to comparable medications in placebo-controlled trials--that is, whether study design significantly affects treatment outcome. Sixteen studies (nine comparator trials and seven placebo-controlled trials) met the rigorous inclusion criteria for the meta-analysis. As hypothesized, antidepressant response rates were significantly higher in the comparator trials compared with placebo-controlled trials; the estimated probability of antidepressant response in a placebo-controlled trial was 46% as compared with 60% in a comparator trial. The results of the study suggest that when clinicians want to make evidence-based treatment decisions and communicate likelihood of response to patients, data from comparator trials may be more appropriate than results of placebo-controlled trials.

Tricyclic Antidepressants

Although perhaps used much less in younger patients, the TCAs, specifically nortriptyline, continue to be an important option in the treatment of late-life depression. Although the preponderance of studies examining TCA treatment in late-life depression do not use plasma level measurements, the findings of these studies have established TCAs to be an effective treatment for depression in older adults.

Nortriptyline.

Of the TCAs, nortriptyline has been found to induce the least orthostatic hypotension and has a documented "therapeutic window" that permits optimal dosing (Roose *et al.* 1981). Consequently, nortriptyline has emerged as the choice of this class of medications for late-life depression. However, there are no rigorous placebo-controlled trials of nortriptyline in late-life depression; thus, the relative effectiveness of this medication is inferred from two open trials and three randomized comparator trials.

In a study reported by Flint and Rifat (1996), 101 patients with symptoms meeting DSM-III-R criteria for major depressive disorder (MDD) (American Psychiatric Association 1987) were treated openly with nortriptyline. The dosing schedule was as follows: all patients achieved a daily dosage of 75 mg by the end of week 1, and then the dosage was adjusted, if necessary, to achieve a plasma level within the therapeutic window of 50-150 ng/mL. The treatment duration was 6 weeks, and the remission criterion was a 17-item Hamilton Rating Scale for Depression (Ham-D-17) final score of 10 or less; 60% of the intent-to-treat sample and 75% of the completers met the remission criterion. To establish speed of response, the authors determined the week of treatment that the 61 patients who met the criterion for remission at the end of the study first achieved sustained remission. Not surprisingly, at the end of week 1, no patient met the criterion for remission, and thus the cumulative response rate was 0%. At week 2, 11% of the sample met the remission criterion, and at week 3, 33% met the remission criterion (thus, the cumulative rate at the end of week 3 was 11% + 33%, or 44%). At weeks 4 and 5, 25% and 20%, respectively, met the remission criterion. Thus, the accumulated remission rate at the end of week 5 was 89%. Although it is widely believed that individuals with late-life depression should have longer treatment trials, specifically 12 weeks, this study found that 89% of the patients who eventually recovered did so by the end of week 5. A second open study of a therapeutic plasma level of nortriptyline reported on 42 inpatients (mean age = 70 years) with cardiac disease and melancholic depression who also were treated for 6 weeks (Roose *et al.* 1994). The remission criterion was a 21-item Ham-D (Ham-D-21) final score of 8 or less; the intent-to-treat remission rate was 67%, the completer remission rate was 82%, and the dropout rate was 19%.

Three randomized controlled studies compared nortriptyline with an SSRI, two studies compared nortriptyline at a therapeutic plasma level with paroxetine, and one study compared flexible-dosage nortriptyline with sertraline. Mulsant *et al.* (2001a) compared nortriptyline with paroxetine in 116 inpatients and outpatients (mean age = 72 years) in a 12-week trial. Remission was defined as a final Ham-D-17 score of 10 or less; the intent-to-treat remission rate was 57% for the nortriptyline group and 55% for the paroxetine group. The rate of dropout due to side effects in the nortriptyline group was significantly higher than that in the paroxetine group (33% vs. 16%; $P = 0.04$).

A second randomized controlled trial comparing nortriptyline (targeted to a therapeutic plasma level) with paroxetine is included in this chapter, although technically it should not be considered a geriatric study because the mean age of the patients was 58 years (Nelson *et al.* 1999). However, it is the only other study comparing a TCA at a therapeutic plasma level with an SSRI, and the results are consistent with those of the Mulsant *et al.* (2001a) study. In this trial, 81 outpatients with ischemic heart disease were treated with medication for 6 weeks. The remission criterion was a final Ham-D-17 score of 8 or less; in the intent-to-treat analysis, 63% of the nortriptyline group and 61% of the paroxetine group were remitters. The dropout rate for nortriptyline (35%) was significantly higher than the dropout rate for paroxetine (10%) ($P < 0.05$). The rate of remission in study completers was 85% for nortriptyline and 68% for paroxetine--a difference that was not statistically significant, although the power of this comparison was limited by the small size of the completer group.

The randomized controlled trial comparing sertraline with nortriptyline included 210 patients (mean age = 68 years) randomly assigned to 12 weeks of medication treatment

(Bondareff *et al.* 2000). Response was defined as a 50% reduction in the 24-item Ham-D (Ham-D-24) score from baseline. Response rates for nortriptyline and sertraline were 41% and 52%, respectively; remission rates were not reported.

TCA side effects and safety. The clinical utility of TCAs in the late-life population is limited by their side-effect and safety profiles. TCAs have significant anticholinergic effects that result in dry mouth, constipation, urinary retention, and confusional states. In addition, TCAs are lethal in overdose, and as little as three times the daily dosage can result in death from heart block or arrhythmias (Glassman *et al.* 1993). The TCAs have type 1A antiarrhythmic activity similar to that of moricizine and quinidine and consequently are presumed to confer an increased risk of sudden cardiovascular death if given to patients with ischemic heart disease. Given the prevalence of occult and manifest ischemic heart disease in individuals older than 60 years, the use of TCAs in this population must reflect a careful consideration of the risk-benefit ratio.

Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors

As in younger depressed patients, the SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the most commonly prescribed antidepressant classes for late-life depression. Within the SSRI class, the various medications appear to have equivalent efficacy and side-effect profiles. There are differences in pharmacokinetics and potential for drug-drug interactions, which are of importance in the geriatric population and have been discussed earlier in this chapter.

A meta-analysis of 12 placebo-controlled trials of antidepressants, including SSRIs, SNRIs, and bupropion, for the treatment of MDD in patients older than 60 years found an overall odds ratio (OR) of 1.43 (95% CI = 1.24, 1.65; $P < 0.0001$), showing medications to be significantly more effective than placebo; the response rate with medication was 46% compared with 30% for placebo (Nelson 2019; Tedeschini *et al.* 2011). However, there was considerable heterogeneity in treatment response, suggesting that there may be other factors besides the antidepressant medication that could account for the difference in the treatment groups. This meta-analysis reported than the number needed to treat (NNT) between drug and placebo was 10.

While the NNT was developed to facilitate the practice of evidence-based medicine, the use of the NNT to quantify the difference between medication and placebo raises a question about the evidence that can be extended from the clinical trial to the clinical situation. Placebo was assumed to be therapeutically inert in the original formulation of the NNT, but more recent data for conditions such as MDD suggest that assignment to placebo group can have considerable therapeutic effects. The NNT calculated from randomized controlled trials reflects a comparison between medication plus clinical management and placebo plus clinical management, whereas in the clinical setting physicians choose between prescribing open medication, observing a patient over time with a supportive approach, and doing nothing. Thus, NNTs derived from clinical trials are not always relevant to clinical decision-making, because they are based on control conditions that do not exist in standard practice.

Specific medications. ***Fluoxetine.*** Four large studies of fluoxetine in late-life depression have been conducted: 1) a placebo-controlled study (Tollefson *et al.* 1995);

2) a three-cell study comparing venlafaxine, placebo, and fluoxetine (Schatzberg and Cantillon 2000; see "Venlafaxine" below); 3) a randomized controlled trial with a comparator, sertraline (Newhouse *et al.* 2000); and 4) an open-treatment study of fluoxetine (Mesters *et al.* 1992). In the first study, fluoxetine (20 mg/day for 6 weeks) was compared with placebo in 671 patients (Tollefson *et al.* 1995). The intent-to-treat analysis remission rate (Ham-D-17 score [?] 7 after 4 weeks) was 23% for fluoxetine and 13% for placebo; in the completer analysis, the remission rate was 27% for fluoxetine and 16% for placebo. Although fluoxetine was significantly more effective than placebo in both the intent-to-treat and the completer analyses, the remission rates in this study were disappointingly low in comparison to the clinical experience with therapeutic plasma levels of TCAs.

In the comparator randomized clinical trial, patients were randomly assigned to receive either fluoxetine 20-40 mg/day or sertraline 50-100 mg/day for 12 weeks (Newhouse *et al.* 2000). The sample of 225 patients (mean age = 68 years) was somewhat unusual because the mean duration of the current episode of major depressive disorder was 9 years. The intent-to-treat remission rate was 46% for fluoxetine and 45% for sertraline, the completer remission rate was 60% for fluoxetine and 59% for sertraline, and the dropout rate was 33% for fluoxetine and 32% for sertraline. This study also reported an intriguing analysis of the response pattern of a subsample of 75 patients (42 treated with sertraline, 33 treated with fluoxetine) with a mean age of 75 years. For both sertraline and fluoxetine, 95% of the patients who achieved a 50% reduction in baseline Ham-D score did so by the end of week 8. As with the Flint and Rifat (1996) study of a therapeutic plasma level of nortriptyline, these data challenge the clinical wisdom that antidepressant trials in late-life depression must be extended to 12 weeks.

Finally, 308 patients with symptoms meeting DSM-III (American Psychiatric Association 1980) criteria for MDD (mean age: 66 years) were treated openly with 20 mg/day of fluoxetine for 8 weeks (Mesters *et al.* 1992). The remission criterion was a final Ham-D-24 score of 10 or less; the intent-to-treat remission rate was 35%, the completer remission rate was 50%, and the dropout rate was 29%.

***Sertraline*.** In addition to the two randomized controlled comparator trials previously described (nortriptyline vs. sertraline and fluoxetine vs. sertraline), a large rigorous placebo-controlled trial of sertraline in late-life depression was completed (Schneider *et al.* 2003). In this study, 716 patients (mean age = 70 years) were randomly assigned to flexible-dosage sertraline (50-100 mg/day) or placebo in an 8-week clinical trial. The criterion for remission was a final Ham-D-17 score of 10 or less; the intent-to-treat remission rate was 29% in the sertraline group, compared with 23% in the placebo group ($P < 0.05$).

***Paroxetine*.** Two previously described trials, by (Mulsant *et al.* (2001a) and Nelson *et al.* (1999), compared nortriptyline at a therapeutic plasma level with paroxetine, with intent-to-treat remission rates (final Ham-D-17 score [?] 10) for the paroxetine groups of 55% and 61%, respectively. In a third trial, 255 patients (mean age = 72 years) were randomly assigned to receive mirtazapine 30-45 mg/day or paroxetine 30-40 mg/day in an 8-week clinical trial (Schatzberg *et al.* 2002). The criterion for remission was a final

Ham-D-17 score of 7 or less; the intent-to-treat remission rates were 38% for mirtazapine and 28% for paroxetine and were not statistically different.

***Citalopram and escitalopram*.** Many of the studies of citalopram in a geriatric population included patients with depression and dementia or significant cognitive impairment; therefore, the results of these studies are not comparable to those of other antidepressant trials in late-life depression (Gottfries 1996). However, two studies have provided information on citalopram in this population; the first was a single-blind comparison between citalopram and nortriptyline (the latter at therapeutic plasma levels), and the second was a comparison of citalopram with placebo in depressed patients older than 75 years.

In the first study, 58 patients (mean age = 71 years) were randomly assigned to treatment with either citalopram at a dosage of 30-40 mg/day or nortriptyline at a therapeutic plasma level in a 12-week clinical trial (Navarro *et al.* 2001). The criterion for remission was a final Ham-D-17 score of 7 or less; the intent-to-treat remission rate was 69% for citalopram and 93% for nortriptyline. The remission rates for both medications were strikingly high in comparison with those in other trials; whether this result derived from differences in patient population or differences in study design is not obviously apparent.

The second trial is unique in the literature because it is the only study to focus on treatment of depression in the "old-old." In this study, 174 patients were randomly assigned to treatment with either citalopram 20-40 mg/day or placebo in an 8-week clinical trial (Roose *et al.* 2004). The population was 58% female, with a mean age of 80 years and a mean baseline Ham-D-24 score of 24. The intent-to-treat response rate (50% reduction from baseline Ham-D score) was 41% in the citalopram group and 39% in the placebo group. The sample was divided for secondary analyses into patients with "severe" and "not severe" depression, which were defined as being either above or below the mean Ham-D score, respectively. The "not severe" group had a baseline Ham-D score of 22 and included 47 patients randomly assigned to receive citalopram and 59 patients randomly assigned to receive placebo. In this group, the intent-to-treat remission rate (Ham-D score [?] 10) was 34% for citalopram and 41% for placebo. The "severe" patient group had a mean baseline Ham-D score of 28 and included 37 patients randomly assigned to receive citalopram and 31 patients randomly assigned to receive placebo. In this group, the intent-to-treat remission rate was 36% for citalopram and 19% for placebo. Thus, citalopram was significantly more effective than placebo in the "severe" patient population, but this difference resulted not from an increased efficacy of citalopram compared with "not severe" patients but rather from a decreased efficacy of placebo.

A third study--an 8-week randomized controlled trial--compared citalopram (flexible dosage of 10-20 mg/day) and venlafaxine (flexible dosage of 75-150 mg/day) in the treatment of late-life depression (Allard *et al.* 2004). The study included 151 patients (mean age = 73 years; 73% female) with a mean baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of 27 +- 4. The response rates for venlafaxine versus citalopram were 75% and 73%, respectively, and the remission rates were 19% and 23%, respectively. The differences between the response rates and the remission rates were quite striking; it is unusual to see such a differential.

There are two randomized controlled trials of escitalopram in the treatment of late-life depression. In one study, 517 patients (mean age = 75 years; 75% female; mean baseline MADRS score = 28 +- 4) were randomly assigned to receive escitalopram (10 mg/day), fluoxetine (20 mg/day), or placebo. There was no significant difference in response rates

across the three treatment conditions (response rates: escitalopram 46%, fluoxetine 37%, and placebo 47%) (Kasper *et al.* 2005). In a separate 8-week randomized, placebo-controlled trial of escitalopram (*N* = 264 patients; mean age = 68), the study failed to find a statistically significant difference in the primary measure of depression outcome (Bose *et al.* 2008). The dropout rate was 19% for escitalopram and 26% for placebo.

Venlafaxine. Only one available study provides meaningful information about venlafaxine in a geriatric population (Schatzberg and Cantillon 2000). In this randomized controlled clinical trial, 204 patients (mean age = 71 years) were randomly assigned to treatment with venlafaxine (75-225 mg/day), fluoxetine (20-60 mg/day), or placebo. The intent-to-treat remission rate (Ham-D-24 score [?] 8) was 42% for venlafaxine, 29% for fluoxetine, and 38% for placebo (no statistically significant differences). Significantly more patients treated with venlafaxine (27%) and fluoxetine (19%) discontinued study participation because of side effects than did those given placebo (9%) ($P < 0.05$). Cardiovascular measures, including heart rate and measures of cardiac conduction (including pulse rate, QRS, and QTc intervals), were assessed, and neither medication induced a significant change compared with placebo in any of these measures.

Duloxetine. In the one randomized controlled trial of duloxetine for the treatment of late-life depression, 311 patients (mean baseline Ham-D score = 22) were randomly assigned in a 2-to-1 allocation favoring duloxetine (Raskin *et al.* 2007). The response and remission rates were significantly greater for duloxetine than for placebo (response rates: duloxetine 37%, placebo 27% [$P < 0.001$]; remission rates: duloxetine 19%, placebo 15% [$P = 0.002$]). However, as with many other trials of antidepressant medication for the treatment of late-life depression, the remission rates were distressingly low.

SSRI side effects and safety. As a group of medications, the SSRIs have the same side-effect profile in older individuals as in younger ones--specifically, gastrointestinal distress, agitation, insomnia, and sexual dysfunction. Discontinuation rates for SSRIs are not statistically different from the discontinuation rates reported for nortriptyline after a therapeutic plasma level had been achieved in the geriatric samples.

With respect to safety, the SSRIs offer a significant advantage over the TCAs. SSRIs are relatively benign in overdose (Barbey and Roose 1998) and do not have an effect on blood pressure, heart rate, cardiac conduction, or cardiac arrhythmias (Glassman *et al.* 2002; Roose *et al.* 1998). However, hyponatremia is a side effect that occurs primarily in older patients. This side effect has been illuminated in observational studies, and the results are variable (De Picker *et al.* 2014). A study using the Danish National Registry suggested that the frequency of hyponatremia was highest during the first 14 days following the initiation of treatment. One study reported that use of an SSRI (compared with no use) was associated with a fivefold increase in the rate of hospitalization for hyponatremia, although the absolute increase was only 1.3% (Gandhi *et al.* 2017). Although uncommon, a confusional state can result from hyponatremia, and this potential cause should be considered when a patient's mental status changes while taking an SSRI.

SSRIs, SNRIs, and risk of bleeding. Studies of SSRI treatment show that after weeks of SSRI administration there is a consistent and significant reduction in platelet serotonin content, which is in the range of 65%-90% of the level seen in controls (Maurer-Spurej *et al.* 2004) However, studying the consequences of this serotonin reduction for platelet activation, bleeding time, and clotting time is a complex undertaking that is highly sensitive to methodological factors. Perhaps as a result, the data reported from such studies are mixed, but in general it appears that reducing the serotonin content in platelets significantly decreases both platelet secretory response and platelet aggregation, leading to decrements in platelet plug formation (Hergovich *et al.* 2000; Tseng *et al.* 2010). As a rough approximation, the SSRIs can be considered to have an "anti-platelet" effect similar in magnitude to that of aspirin (Kotzailias *et al.* 2006)

Systematic, replicated research has revealed an association between SSRI treatment and risk of upper gastrointestinal (UGI) bleeding and intracerebral hemorrhage in older adults (Hackam and Mrkobrada 2012). Several studies examining the association between UGI bleeding and the use of SSRIs or SNRIs have observed increased relative risks (RRs) for UGI bleeding associated with medication use compared with nonuse. For example, patients treated with SSRI medication were 1.7 times more likely to experience UGI bleeding (95% CI = 1.4-2.0) compared with non-SSRI users (Dall *et al.* 2009). To further examine this association, a retrospective study obtained data (from a voluntary, fee-supported database) on all patients older than 18 years who had undergone major surgery between January 1, 2006, and December 31, 2008, at 375 U.S. hospitals (Auerbach *et al.* 2013). Among the 530,416 patients identified, 72,450 had received an SSRI in the perioperative period, as documented by the hospital pharmacy records. Patients receiving an SSRI had a greater risk of bleeding (OR = 1.9; 95% CI = 1.04-1.15; number needed to harm [NNH] = 424) and a higher mortality rate (adjusted OR = 1.20; 95% CI = 1.07-1.36; NNH = 839) than patients who were not receiving an SSRI. In addition, the 23,395 patients taking SNRI medication appeared to have the same outcomes as the SSRI-treated patients.

Other Agents With Antidepressant Effects

Mirtazapine. As previously discussed, in one randomized controlled comparator trial of mirtazapine versus paroxetine in a geriatric population, the intent-to-treat remission rate was 38% for the mirtazapine group and 28% for the paroxetine-treated patients (Schatzberg *et al.* 2002). In this study, the rate of discontinuation due to adverse events was similar in both groups: 33% for mirtazapine and 29% for paroxetine.

Bupropion. One randomized controlled comparator trial of bupropion versus paroxetine in late-life depression has been published, and this represents the only data available on bupropion in this population (Weihs *et al.* 2000). In this 6-week clinical trial, 100 patients (mean age = 70 years), with a mean baseline Ham-D-24 score of 27, were randomly assigned to treatment with either bupropion (100-300 mg/day) or paroxetine (10-40 mg/day). The rate of response (defined as a 50% reduction from baseline Ham-D score) in the intent-to-treat analysis was 71% in the bupropion group and 77% in the paroxetine group. Remission data were not reported. The discontinuation rate was 17% in the bupropion group and 15% in the paroxetine group.

A second study of bupropion in late-life depression randomly assigned 418 patients (mean age = 71 years) to a 10-week trial of placebo or active drug. The study failed to find a statistically significant difference in the primary measure of outcome, although some secondary measures favored drug over placebo. The dropout rate was not different between the two treatment groups (Hewett *et al.* 2010).

Quetiapine. In one study of quetiapine monotherapy in late-life MDD, 338 patients (mean age = 71 years) were randomly assigned to receive quetiapine (mean dose = 159 mg; range = 50-250 mg) or placebo in an 8-

week trial. Interestingly, reduction in depressive symptoms was significantly greater in the quetiapine group than in the placebo group, with a response rate of 64% (vs. 30% for the group receiving placebo) and a remission rate of 56% (vs. 23% of those receiving placebo). Not surprisingly, the most notable side effect was somnolence, with a dropout rate from side effects of 10% in the quetiapine group compared with 4% in the placebo group (Katila *et al.* 2013).

Duration of Treatment

The belief that patients with late-life depression take longer to respond than younger patients has led to the dictum that for older patients, the minimum duration necessary for an adequate antidepressant trial is 12 weeks. However, it is currently unclear whether all patients require a 12-week trial before they can be considered nonresponders, because data on this topic have been sparse and somewhat contradictory. For example, a patient who is very symptomatic at week 11 is unlikely to improve dramatically and meet remission criteria by week 12.

Two industry-sponsored 12-week randomized controlled trials of SSRIs in late-life depression comparing sertraline with nortriptyline and sertraline with fluoxetine both reported an increase in response rates at week 12 compared with week 8 (Bondareff *et al.* 2000; Newhouse *et al.* 2000). In the first study, 236 patients were randomly assigned to treatment with either fluoxetine or sertraline for 12 weeks. In the second study, 210 patients were randomly assigned to treatment with either sertraline or nortriptyline for 12 weeks. However, analyses of most 12-week antidepressant trials in late-life depression focused on time to response, and the early identification of nonresponders may be more useful to clinicians (Sackeim and Roose 2002).

Because patients who completed the two trials described above did not differ in demographic or clinical features, nor did the groups differ in rates of response or remission, the four groups were combined for the purpose of enhancing sample size with respect to other analyses (Sackeim and Roose 2002). For the total sample of completers ($N = 304$), the response rate was 69%. When the criterion for remission was a final Ham-D-24 score [?] 10, the remission rate was 59%. Although the median time to onset of sustained remission was 4 weeks, 36% of the patients required 8 weeks or longer to reach this point. However, if the remission criterion was a final Ham-D score [?] 6, then the time to sustained remission was 8 weeks, with 29% of the patients reaching the criterion only in week 12. Such findings are consistent with a view in which time to remission is dependent on the remission criteria. However, neither the overall response or remission rates nor the time to achieve sustained remission in this study supports the belief that patients with late-life depression are less responsive to antidepressant medication or take longer to respond (Sackeim and Roose 2002).

On the basis of these results, if a patient does not have at least a 30% improvement in the Ham-D score by week 2, they have only a 22% probability of being in remission at week 12 (using the remission criterion of a Ham-D score [?] 6). This probability progressively decreases, so that by week 6, if a patient does not have a 30% reduction in baseline Ham-D score, the probability of remission at the end of week 12 is only 7%. These results suggest that if there is not a moderate degree of symptomatic improvement early in treatment, clinicians can have a high level of accuracy in predicting that the patient will not adequately respond to this treatment within 12 weeks.

Therefore, the most important clinical implication of these data is that clinicians do not have to give a 12-week trial of antidepressant medication to all older depressed patients. Rather, they can make informed decisions about changing or continuing treatment at the 4-and 6-week time points based on the probability that given the patient's improvement to date, the remission criterion will or will not be met by week 12.

Augmentation of Antidepressant Treatment

If a trial of an antidepressant has failed, it is now common practice to try a second trial of monotherapy with a second antidepressant, often from a different class of medication, or to augment the antidepressant. There are data that support augmentation with aripiprazole, lithium, or methylphenidate.

A study of lithium augmentation in older patients compared response rates after 4 weeks in 145 younger (< 65 years) versus 22 older ([?] 65 years) patients with unipolar MDD. Although the older patients had a significantly higher response rate, the clinical utility of lithium in older adults could not be evaluated because there were no data on adverse events and side effects (Buspavanich *et al.* 2019).

Although stimulants are widely used in late-life depression, there is a paucity of data to support their use. In one notable study, 143 older adults with MDD (mean age = 70) were randomly assigned to receive 16 weeks of treatment with methylphenidate (mean dosage = 16 mg/day) plus placebo, citalopram (mean dosage = 32 mg/day) plus placebo, or a combination of both active medications. The decrease in Ham-D score was greater in the citalopram-methylphenidate group, as was the remission (Ham-D score < 6) rate (62%, compared with 42% in the citalopram-placebo group and 29% in the methylphenidate plus placebo group). Importantly, the three groups did not differ in number of side effects or dropout rate (Lavretsky *et al.* 2015).

A more recent strategy is the use of atypical antipsychotics to augment an antidepressant. One well-designed study compared the effectiveness of aripiprazole with placebo in older patients with MDD who did not respond to a trial of venlafaxine at a dosage of 150-300 mg/day for 12 weeks (Lenze *et al.* 2015). In the 181 of 468 participants (38% of the sample) who did not have their symptoms remit while taking venlafaxine, 91 were randomly assigned to receive augmentation with aripiprazole (2-15 mg/day) or placebo for 12 weeks. The researchers found a significantly greater remission rate in patients treated with aripiprazole (44%) compared with those given placebo (29%). The early discontinuation rate was 5% and did not differ between the treatment conditions. The most significant side effect was akathisia, which was observed in 27% of patients randomly assigned to receive aripiprazole vs 12% of those randomly assigned to receive placebo. However, the akathisia was reported as mild and did not persist.

Treatment-Resistant Depression in Older Adults

Treatment-resistant depression (TRD; two failed trials of antidepressants) in older adults is a leading cause of disability, excess mortality from suicide, and dementia. Although TRD in older adults is common, there are few data to guide more accessible pharmacological strategies other than intravenous ketamine and electroconvulsive therapy (ECT).

Intravenous ketamine, an anesthetic agent that blocks *N*-methyl-D-aspartate (NMDA) glutamate receptors, has substantial benefits for mood, quality of life, and reduced suicidality, and is fast and effective for TRD. Randomized controlled trials (using placebo or midazolam control) show that a 0.5-mg IV infusion given over 40 minutes provides a rapid antidepressant response, and its likelihood is undiminished by prior antidepressant failures (Coyle and Laws 2015). Meta-analyses have examined the antidepressant effect of intravenous ketamine, the largest of which included 21 studies and 437 TRD patients (Coyle and Laws 2015), finding a significant and rapid reduction of depressive symptoms after a single intravenous infusion of ketamine. However, the safety and efficacy of ketamine in older adults are poorly understood because such studies have excluded adults ages 65 years and older.

The available data on ketamine use in older individuals with TRD are from a case series of 53 patients (mean age = 67 years), who received four ketamine infusions over 2 weeks (Lipsitz *et al.* 2021). A response rate of 27% was reported (with response defined as > 50% reduction from the baseline Quick Inventory of Depressive Symptomatology [QIDS] score). However, perhaps the most revealing information from this series was the side effect and safety data. During ketamine infusions, 36 participants (69%) experienced treatment-emergent hypertension, which in general resolved after 20 minutes and was more frequent among patients with preexisting hypertension. Therefore, the management of blood pressure during ketamine infusion has emerged as the key safety issue for patients, particularly among those with baseline hypertension. Otherwise, the ketamine infusions were well tolerated, with the most frequent reported side effects being transient drowsiness, dizziness, and confusion.

The recent FDA approval of esketamine highlights the paucity of data on late-life TRD. There were two Phase III randomized placebo-controlled trials of esketamine nasal spray in patients age 65 years or older, which demonstrated acute and maintenance efficacy (Ochs-Ross *et al.* 2020).

However, a 4-week randomized, double-blind, placebo-controlled trial for TRD in patients age 65 years or older ($N = 138$) failed to show a statistically significant treatment difference between esketamine and placebo (weighted combination test two-sided $P = 0.06$) (Ochs-Ross *et al.* 2020). A planned subgroup analysis showed greater improvement in depression among participants in the esketamine group who were age 65-74 years and among those with an onset of depression before age 55 years. Fortunately, there were no serious adverse events reported. Overall, given the limited available data on efficacy and safety of intravenous ketamine and esketamine in late-life TRD, there is a compelling need for large, well-designed controlled trials.

The recent publication of the results of the OPTIMUM study offers a valuable guide for the evidence-based treatment of TRD (Lenze *et al.* 2023). This study enrolled 619 patients older than 60 years with TRD who were first randomly assigned (Step 1) to one of the following conditions for 10 weeks: 1) augment current antidepressant with aripiprazole (up to 15 mg/day), 2) augment current antidepressant with bupropion (up to 450 mg/day), or 3) switch current antidepressant to bupropion 450 mg/day. If the remission criterion of a MADRS score lower than 10 was not met after Step 1, patients entered Step 2 and were randomly assigned to receive lithium augmentation or nortriptyline adjusted to a therapeutic plasma level. Remission occurred in 28.9% of the aripiprazole augmentation group (risk ratio [RR] vs. the switch-to-bupropion group, 1.50; 95% CI, 1.06 to 2.13), 28.2% of the bupropion augmentation group (RR, 1.49; 95% CI, 1.04 to 2.12), and 19.3% of the switch-to-bupropion group (RR, 1.00 [reference]). Such remission rates were not only statistically significant but also clinically meaningful, given the low response rates typically seen in TRD. Interestingly, the rate of falls was highest in the bupropion augmentation group (0.55 falls per patient in bupropion augmentation, 0.33 falls per patient in aripiprazole augmentation, and 0.38 falls per patient in switch to bupropion) and included many injurious falls. In Step 2, there were no differences among groups in remission rates or falls. Remission occurred in 18.9% of patients in the lithium augmentation group and 21.5% in the switch-to-nortriptyline group. Overall, given the high rates of falls in the bupropion augmentation group, such results suggest that in this population with TRD, aripiprazole augmentation may be a better overall antidepressant strategy than either bupropion augmentation or a switch to bupropion (Lenze *et al.* 2023).

Antipsychotics in Older Adults

Neuropsychiatric symptoms are nearly ubiquitous in older adults with dementia, and about half of patients with Alzheimer's dementia develop agitation (Anatchkova *et al.* 2019). Antipsychotics and other psychotropic medications are used widely in the management of dementia-related psychosis or agitation because there are limited treatment alternatives; evidence for the effectiveness of nonpharmacological behavioral approaches is limited and may apply mainly to patients with mild behavioral symptoms.

The prevalence of dementia is approximately 2%-5% among adults older than 60 years, and antipsychotic use in neurocognitive disorders exceeds antipsychotic use in psychotic disorders due to the difference in disease prevalence rates (Colenda *et al.* 2002). Whereas the prevalence of schizophrenia in older adults remains below 1%, the prevalence of neurocognitive disorders increases to 15%-40% among adults older than 85 years (Thomas *et al.* 2001).

Special Safety Considerations in Older Patients

Antipsychotic Side Effects

Older patients can be more sensitive to the side effects of antipsychotics, which can include sedation, cardiac effects (e.g., tachycardia, orthostatic hypotension), anticholinergic side effects (e.g., dry mouth, blurred vision, constipation, urinary retention), cognitive effects, extrapyramidal symptoms, neuroleptic malignant syndrome, autonomic instability, and seizures.

Although most antipsychotics can cause orthostatic hypotension, it is most often observed with low-potency typical (conventional) antipsychotics such as chlorpromazine and thioridazine and atypical antipsychotics such as clozapine, risperidone, olanzapine, and quetiapine. Likewise, low-potency typical antipsychotics and clozapine have the greatest potential to cause anticholinergic effects. To varying degrees, the metabolic syndrome with glucose dysregulation is a potential side effect of all antipsychotic medications. Type 2 diabetes mellitus or diabetic ketoacidosis may be more common with clozapine and olanzapine compared with other antipsychotics, and blood glucose levels need to be monitored in elderly individuals (Jin *et al.* 2004). However,

one retrospective chart review in geriatric inpatients observed atypical antipsychotics to be generally weight neutral, suggesting that antipsychotic-induced weight gain may be more of a concern in younger adults than in older adults (Yeung *et al.* 2017).

The numbers of available dopamine neurons and dopaminergic receptors decrease with aging (Costa 2014), which may reduce the tolerance of elderly patients to antipsychotics, thus increasing the likelihood of neurological side effects such as extrapyramidal side effects (EPS) and tardive dyskinesia (TD). For example, Saltz *et al.* (1991) reported an incidence of TD of 31% after 43 weeks of typical antipsychotic treatment in a sample of elderly patients, and antipsychotic-induced TD is five to six times more prevalent in elderly individuals compared with younger ones (Jeste 2000). Atypical antipsychotics are more potent antagonists at the serotonin type 2A (5-HT$_{2A}$) receptor than at the dopamine D$_2$ receptor, resulting in fewer EPS and less TD compared with typical antipsychotics (Jeste *et al.* 1999). However, EPS emerging during risperidone use can be observed at much lower D$_2$ occupancies in older adults than in younger adults (33%-79% vs. > 80%) (Leon *et al.* 2010). Therefore, it has been proposed that neurological side effects may be more related to the absolute--as opposed to the relative (i.e., percentage)--number of occupied D$_2$ receptors. For this reason, the higher susceptibility of older patients to the neurological side effects of EPS and TD requires the use of dosages lower than those commonly used in young adults.

Sedation is one of the most common side effects of antipsychotic medications. Low-potency antipsychotics can be potent sleep inducers and have a greater propensity to cause anticholinergic side effects, which can lead to daytime confusion and disorientation in older persons. Antipsychotic use has also been associated with acute kidney injury in older adults, although the mechanism underlying this effect is not clear (Hwang *et al.* 2014). Lastly, there have been reports of an association between antipsychotic use and deep vein thrombosis in dementia, which may be related to the decrease in mobility and sedative effect of several antipsychotics (Parker *et al.* 2010).

Antipsychotic Effects on Cognition and Activities of Daily Living

All antipsychotic medications can have cognitive side effects, but the anticholinergic activity of antipsychotics may further compromise the already damaged central cholinergic projections in Alzheimer's disease. In parallel, sedation produced by antipsychotics may worsen the degree of disorientation and cognitive impairment in dementia. For example, among outpatients with Alzheimer's disease in the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) trial, those who received atypical antipsychotics showed a greater decline in cognitive function, at a level consistent with 1 year's deterioration, in comparison with those who received placebo (Vigen *et al.* 2011). Such effects may be worsened by the use of antipsychotics with strong anticholinergic properties or by the addition of anticholinergic agents to treat drug-induced EPS. Therefore, if EPS develops following antipsychotic treatment in a patient with dementia, switching to an antipsychotic that is less likely to cause EPS is preferable to adding an anticholinergic medication to treat the EPS.

Antipsychotic Mortality Risks

The use of antipsychotics is associated with a dose-related increased risk of sudden cardiac death (Ray *et al.* 2009). Antipsychotic medications may block repolarizing potassium currents and prolong the QTc interval, which is associated with the development of torsades de pointes and sudden death (Goodnick *et al.* 2002). On the basis of a review of double-blind, placebo-controlled trials of atypical antipsychotics in patients with dementia, the FDA concluded that there was a significantly greater mortality risk (1.6-1.7 times) for patients treated with these medications compared with those receiving placebo, and that all antipsychotic medications must carry a black box warning to this effect (Jeste *et al.* 2008; Schneider *et al.* 2005). However, the absolute increased risk with short-term treatment is estimated to be relatively small (1%-2%).

There is no clear explanation as to why the use of antipsychotics is associated with an increased mortality risk specifically in patients with dementia. There may be a small increase in the risk of stroke for atypical antipsychotics (Brodaty *et al.* 2003), but the stroke risk is unlikely to be the sole factor leading to the increased mortality risk (Jeste *et al.* 2008). The increased risk of mortality may also be due to cardiac and metabolic side effects, hip fracture, cognitive worsening, falls, or pneumonia (Steinberg and Lyketsos 2012; Watt *et al.* 2020).

Studies comparing the mortality risk of various antipsychotics have not been conclusive. Whereas some analyses have observed increased incidence of cardiac arrhythmias and mortality among those taking typical antipsychotics, others have found no differences in outcomes between typical and atypical antipsychotics. In a large-scale medical records study involving more than 75,000 nursing home patients receiving antipsychotics, haloperidol was associated with the greatest increase in mortality risk, risperidone and olanzapine with an intermediate increase in risk, and quetiapine with the lowest increase in mortality risk (Huybrechts *et al.* 2012). Others have replicated this finding, with the caveat that some patients receiving higher dosages of haloperidol were being treated for delirium, which may have artificially increased the mortality rate observed because of the known association between delirium and increased mortality (Maust *et al.* 2015). Using Minimum Data Set-linked Medicare data, one recent analysis of older adults with depression and Parkinson's disease found that use of certain atypical antipsychotics (olanzapine, asenapine, brexpiprazole, iloperidone, lurasidone, paliperidone, and risperidone) compared with other atypical antipsychotics (aripiprazole, clozapine, or quetiapine) was associated with a higher all-cause mortality, which was mainly mediated by pneumonia (Chekani *et al.* 2020).

In summary, although there appears to be a dose-response relation in mortality risk in older adults, there is no clear evidence that establishes which type of antipsychotic is associated with the greatest risk of mortality. In addition, some studies suggest that the mortality risk in older adults may not be as large as has been believed, although this may be attributed to the decrease in antipsychotic prescribing among elderly patients with dementia with serious medical illness since the FDA black box warning was placed (Hulshof *et al.* 2015).

Antipsychotics in the Management of Behavioral Complications of Dementia

Patients with dementia often develop behavioral disturbances (e.g., agitation, aggression) or psychotic symptoms (e.g., delusions, hallucinations). As used here, the term *behavioral complications* denotes both behavioral disturbances and psychotic features.

Behavioral complications occur in most forms of dementia, lead to considerable burden for caregivers, and are common precipitants of institutionalization. Psychosis and behavioral dyscontrol often coexist in Alzheimer's disease, and treatment with antipsychotics is often prescribed for one or both sets of symptoms.

Personality changes occur early in dementia and include apathy, anhedonia, irritability, inability to pay attention, depression, and loss of emotional connection. In later stages, varying degrees of agitation may occur in more than half of Alzheimer's disease patients in outpatient clinics (Devanand *et al.* 1997) and nursing homes (Cohen-Mansfield *et al.* 1989). Other disinhibited behaviors include pacing, wandering, verbal and physical aggression, repetitive calling out, and screaming. While the prevalence of delusions in Alzheimer's disease varies widely in different samples, paranoid delusions of theft and suspicion are the most frequent types of delusions. Hallucinations, which can be visual or auditory, occur in 5%-15% of patients with dementia. In Alzheimer's disease, a typical hallucination is the conviction that someone else is in the house (i.e., phantom boarder syndrome).

In a series of 235 patients with Alzheimer's disease who were followed prospectively for up to 5 years, approximately half of the patients who manifested paranoid delusions or hallucinations at baseline were likely to manifest the same symptom 6 months later (Devanand *et al.* 1997). However, paranoid delusions or hallucinations were evident at three out of four consecutive visits (in only 10%-15% of patients), which raises the question of how long patients need to continue taking antipsychotics after treatment response.

Assessment of Psychopathology in Alzheimer's Disease

In elderly patients, assessment and treatment of psychopathology should occur after reversible medical conditions (e.g., urinary tract infection, metabolic abnormalities, iatrogenic or medication-induced symptoms) have been ruled out. Because of the impairment induced by many types of dementias, most rating scales have been developed as informant-based interviews. Commonly used rating scales for measurement of neuropsychiatric symptoms of Alzheimer's disease include the Neuropsychiatric Inventory (NPI; Cummings *et al.* 1994), the Neuropsychiatric Inventory--Nursing Home Version (Wood *et al.* 2000), the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD; Reisberg *et al.* 1987), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behavior Rating Scale (Tariot *et al.* 1995), and the Cohen-Mansfield Agitation Inventory (CMAI; Cohen-Mansfield *et al.* 1989). The NPI, which employs a quantitative time-efficient decision-tree approach, is the most widely used scale for evaluating the effects of antipsychotic treatment in individuals with dementia.

Neurobiological Mechanisms of Psychosis in Dementia

Although the precise pathophysiology underlying psychosis in Alzheimer's disease and other dementias is still unknown, neurobiological models have been proposed in recent years. For example, it has been suggested that alterations in dopaminergic, glutamatergic, serotonergic, and cholinergic neurotransmission may contribute to the development of psychosis in this population. 5-HT$_{2A}$ receptor polymorphisms have been significantly associated with the development of hallucinations and delusions in Alzheimer's disease (Nacmias *et al.* 2001; Tang *et al.* 2017). Specific genes, such as *ENPP6*, *SUMF1*, or the *APOE* e4 allele, have been identified as genomic correlates of psychosis in Alzheimer's disease (Ismail *et al.* 2022). In addition, cholinergic agents, including the acetylcholinesterase inhibitors (i.e., donepezil, rivastigmine, galantamine), can reduce neuropsychiatric symptoms in Alzheimer's disease and dementia with Lewy bodies, an effect that may implicate the cholinergic system in the development of psychosis in this population (Cummings *et al.* 2016). Neuroimaging studies have also implicated several brain regions in this process, including one analysis of 39 patients with Alzheimer's disease, which found that intensity of hallucinations was associated with atrophy and brain hypometabolism (on fluorodeoxyglucose-PET) in frontal regions and anterior insula, suggesting that dysfunction in brain regions important for cognitive control and attentional processes may be linked to the development of hallucinations (Blanc *et al.* 2014). Several studies have found that burden of neurofibrillary tangles (Ehrenberg *et al.* 2018) and hyperphosphorylated tau (Murray *et al.* 2014) is associated with extent and severity of neuropsychiatric symptoms in Alzheimer's disease. Finally, some studies have observed increased striatal dopamine (D$_2$/D$_3$) receptor availability among Alzheimer's patients with delusions (Reeves *et al.* 2009).

Overview of Psychotropic Medication Use in Dementia

Studies in the 1970s and early 1980s indicated that nearly half of inpatients with dementia in Veterans Administration hospitals (Prien *et al.* 1975) and in other settings (Michel and Kolakowska 1981) received psychotropic medications, primarily antipsychotics and benzodiazepines (Ray *et al.* 1980). Growing awareness of the neurological side effects of typical antipsychotics, particularly in dementia patients in nursing homes, led to the promulgation of the Omnibus Budget Reconciliation Act (OBRA) of 1987 (Elon and Pawlson 1992). OBRA required identification of target symptoms, justification for the use of antipsychotics, and mandatory attempts to decrease or stop the antipsychotic medication every 3 months. In 2012 the Centers for Medicare and Medicaid Services initiated the National Partnership to Improve Dementia Care in Nursing Homes and began to publicly report data on nursing home quality measures related to antipsychotic use. Nonetheless, antipsychotic medications are widely used and have remained the treatment of choice for behavioral complications in dementia.

Studies of Antipsychotics

In schizophrenia, antipsychotics are often assumed to be specific to the treatment of psychosis, much as improvement in behavioral dyscontrol is believed to be secondary to improvement in psychosis. While the literature is somewhat mixed, in patients with dementia, placebo-controlled studies have shown comparable advantages for antipsychotics over placebo for symptoms of both psychosis and behavioral dyscontrol. In placebo-controlled clinical trials with typical or atypical antipsychotics, response rates have varied between 45% and 60% for active medication and between 20% and 45% for placebo (De Deyn *et al.* 1999; Devanand *et al.* 1998; Street *et al.* 2000; Yury and Fisher 2007), with an overall advantage for antipsychotic over placebo in the range of 18%-26% (Kindermann *et al.* 2002; Ma *et al.* 2014).

Typical antipsychotics. Early placebo-controlled studies of typical antipsychotics used in the management of behavioral complications of dementia showed moderate efficacy with a high placebo response rate, but considerable EPS occurred even at moderate dosages (Finkel *et al.* 1995). No clear superiority has been noted for any particular typical antipsychotic in individuals with dementia. In a double-blind, placebo-controlled, randomized comparison of standard-dosage (2-3 mg/day) and low-dosage (0.50-0.75 mg/day) haloperidol in 71 outpatients with Alzheimer's disease, standard-dosage haloperidol was efficacious and superior to both low-dosage haloperidol and placebo for both psychosis and agitation (Devanand *et al.* 1998). However, EPS tended to be greater for haloperidol (2-3 mg/day) than for the other two conditions. These results suggest a relatively narrow therapeutic window for some typical antipsychotics in dementia patients who develop behavioral complications. If a typical antipsychotic is used, a starting dosage equivalent to haloperidol 0.5 mg/day is advisable, with subsequent titration to achieve an optimal trade-off between efficacy and side effects.

Atypical antipsychotics. Because of their more favorable safety profile, the atypical antipsychotics have gradually replaced typical antipsychotics in the treatment of behavioral complications in dementia. For example, incidence of TD is much lower with atypical antipsychotics than with the typical antipsychotic haloperidol (Jeste *et al.* 2000). In a study of 35 agitated patients with dementia who were switched from haloperidol to risperidone, the crossover was generally safe and effective (Lane *et al.* 2002). In addition, atypical antipsychotics can be safely administered with cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine), which are used to treat the cognitive impairment of dementia (Weiser *et al.* 2002). The choice of atypical antipsychotic depends on the patient's clinical profile and the medication's side-effect profile.

Clozapine. Although clozapine can be more efficacious than other antipsychotics in schizophrenia and carries essentially no risk of TD, several side effects limit its use in patients with dementia and indicate that it should be reserved for those who do not respond to the other available antipsychotics. For example, clozapine causes substantial serotonergic blockade and can have antiadrenergic and antimuscarinic properties (Lieberman 1998). Sedation is common, seizure potential is elevated, and its anticholinergic properties can lead to dry mouth and constipation and can adversely affect cognition in elderly persons. In addition, circulating levels of clozapine rise with age and may be slightly higher in women than in men; sedation is common, and seizure potential is elevated (Centorrino *et al.* 1994; Kurz *et al.* 1998). Intensive monitoring is required for blood dyscrasias, particularly agranulocytosis, which is reported to occur in 0.38% of patients (Kane *et al.* 1988). These factors, as well as the increased risk of falls and fractures related to the side effect of orthostatic hypotension, limit the use of clozapine in older people. The few retrospective reviews and case reports available indicate moderate efficacy but significant adverse events in elderly patients with dementia (Chengappa *et al.* 1995; Pitner *et al.* 1995).

Risperidone. In young adults with schizophrenia, risperidone 6 mg/day has the best therapeutic profile compared with risperidone at lower and higher dosages (Chouinard *et al.* 1993). By contrast, the optimal risperidone dosage range is much lower for elderly persons (Katz *et al.* 1999). Compared with the other atypical antipsychotics, risperidone may be more likely to lead to EPS and TD, although its risk is still considerably lower than that associated with typical antipsychotics such as haloperidol;

in one study, risperidone's 1-year cumulative incidence of TD was a relatively low 2.6% in institutionalized patients with dementia (Jeste *et al.* 2000). Risperidone is mildly sedating and has the potential to cause orthostatic hypotension, although the latter effect is uncommon when low dosages are used in older individuals (Katz *et al.* 1999).

In a multicenter study, 625 nursing home patients with dementia who had behavioral complications were randomly assigned to receive risperidone--at 0.5 mg/day, 1 mg/day, or 2 mg/day--or placebo for 12 weeks (Katz *et al.* 1999). At study endpoint, response rates for risperidone 1 mg/day (45%) and 2 mg/day (50%) were significantly superior to rates for placebo and risperidone 0.5 mg/day, which showed similar response rates (33%). Patients receiving risperidone 2 mg/day were more likely than those receiving risperidone 0.5 mg/day or 1 mg/day to develop EPS and sedation, suggesting a relatively narrow therapeutic window. Therefore, a risperidone starting dosage of 0.5 mg/day in patients with dementia, with gradual upward dosage titration to 1-2 mg/day, is recommended. Its elimination half-life is between 20 and 22 hours, allowing for once-a-day dosing. Although a long-acting injectable risperidone preparation is available, this formulation has not been studied in the treatment of behavioral complications of dementia.

Olanzapine. Sedation and weight gain are prominent side effects of olanzapine, and its use has been associated with the development of metabolic syndrome. However, it has been suggested that atypical antipsychotic-induced weight gain may be more of a concern in younger adults than older adults (Atti *et al.* 2014; Yeung *et al.* 2017). Orthostatic hypotension is not common when low dosages of olanzapine are used in elderly patients (Street *et al.* 2000). Intramuscular olanzapine is a useful alternative to intramuscular haloperidol in the treatment of acutely psychotic, agitated patients with schizophrenia (Breier *et al.* 2002a) and may be a useful alternative to intramuscular lorazepam in patients with dementia (Meehan *et al.* 2002).

In a double-blind, placebo-controlled multicenter clinical trial, 206 nursing home patients with Alzheimer's disease and behavioral complications were randomly assigned to receive placebo or fixed-dosage olanzapine (5 mg/day, 10 mg/day, or 15 mg/day) for 6 weeks. Olanzapine 5 mg/day was significantly more efficacious than placebo, but olanzapine at the 10-mg/day and 15-mg/day dosages was not superior to placebo. Clinically, a starting dosage of 2.5 mg/day at bedtime with gradual upward titration to a target daily dosage of 5-10 mg is recommended.

Quetiapine. In a study of 284 elderly patients with dementia, quetiapine (average dosage = 96.9 mg/day) and haloperidol (average dosage = 1.9 mg/day) were indistinguishable from placebo on most measures of efficacy, although haloperidol led to more EPS (Tariot *et al.* 2006). Wide dosage ranges for quetiapine (from 12.5 to 800 mg/day) are used in clinical practice. Physicians often prescribe quetiapine because of its relatively benign side-effect profile and to take advantage of its main side effect, sedation, in patients who have insomnia. Although it has a short half-life (approximately 3-6 hours [Fulton and Goa 1997]), quetiapine's efficacy has been documented with twice-daily administration. Quetiapine may be started at 25 mg twice daily, with dosage increases as tolerated up to 300 mg twice daily, based solely on clinical response and side effects, because the optimal dosage range for quetiapine has not been identified.

Aripiprazole. In randomized placebo-controlled clinical trials, aripiprazole shows modest efficacy in the treatment of dementia-related psychosis and behavioral disturbances (De Deyn *et al.* 2013), although the literature has been mixed. One placebo-controlled study of aripiprazole in 208 outpatients with behavioral complications of Alzheimer's disease showed no advantage for aripiprazole on the main outcome measure (NPI score), but there was superiority on secondary outcome measures (Brief Psychiatric Rating Scale [BPRS] Psychosis and BPRS Core subscale scores). The average dosage used was 10 mg/day, which was generally well tolerated (De Deyn *et al.* 2005). The optimal dosage for aripiprazole is undetermined, but low starting dosages of 2-5 mg/day can be used.

Brexpiprazole. In May 2023, brexpiprazole was announced as the first FDA-approved treatment option for agitation associated with dementia due to Alzheimer's disease. The effectiveness of brexpiprazole for the treatment of agitation in Alzheimer's disease was determined in two 12-week randomized, double-blind, placebo-controlled, fixed-dose studies. Both found statistically significant and clinically meaningful improvements in key measures of agitation for brexpiprazole over placebo, with a favorable safety and tolerability profile. In the first study, 413 patients were randomly assigned to brexpiprazole 2 mg/day, brexpiprazole 1 mg/day, or placebo (Grossberg *et al.* 2020). Brexpiprazole 2 mg/day (but not brexpiprazole 1 mg/day) achieved significant and clinically meaningful improvement in total CMAI scores compared with placebo at week 12. In the second study, according to data released by the FDA (U.S. Food and Drug Administration 2023), 345 patients were randomly assigned to brexpiprazole 2 mg/day, brexpiprazole 3 mg/day, or placebo. Brexpiprazole 2 mg/day or 3 mg/day demonstrated significant improvements in total CMAI scores compared with placebo. Overall, the recommended starting dosage of brexpiprazole is 0.5 mg once daily on days 1-7, to increase up 1.0 mg daily on days 8-14, and increase to 2 mg daily on day 15. After 14 days, the dosage can be increased to the maximum recommended daily dosage of 3 mg daily, based on clinical response and tolerability. Main side effects include headache, dizziness, urinary tract infection, nasopharyngitis, and sleep disturbances (both somnolence and insomnia). It is worth noting that brexpiprazole still retains the black box warning of an increased risk of death among older patients with dementia-related psychosis.

Comparisons among antipsychotics. Overall, head-to-head comparison studies have shown few differences between typical antipsychotics in the treatment of behavioral complications in dementia (Carlyle *et al.* 1993; Petrie *et al.* 1982). In a study comparing a typical with an atypical antipsychotic, patients with dementia and behavioral complications were randomly assigned to receive flexible-dose risperidone, haloperidol, or placebo (De Deyn *et al.* 1999). In 344 patients, risperidone (mean dose = 1.1 mg/day), haloperidol (mean dose = 1.2 mg/day), and placebo produced no statistically significant differences in improvement rates or psychosis scores at week 12. In post hoc analyses, both haloperidol and risperidone were significantly better than placebo in reducing BEHAVE-AD total scores and CMAI aggression cluster scores, and risperidone was superior to haloperidol on the CMAI aggression cluster scores. However, patients taking haloperidol had significantly higher EPS scores at endpoint than did patients taking either risperidone or placebo, with no significant difference in EPS scores between patients receiving risperidone and those receiving placebo (De Deyn *et al.* 1999). Overall, risperidone's efficacy was comparable to that of haloperidol, but with a superior side-effect profile. In smaller studies in patients with dementia, comparisons of haloperidol and risperidone have yielded equivocal results (Chan *et al.* 2001; Suh *et al.* 2004).

In the 421 elderly patients who participated in the CATIE-AD, which compared risperidone, olanzapine, quetiapine, and placebo (first randomized phase), there were no significant differences in time to discontinuation because the superior efficacy of risperidone and olanzapine was compromised by their increased propensity for side effects; quetiapine was indistinguishable from placebo (Schneider *et al.* 2006). Consistent with these findings, a more recent systematic review found that risperidone, olanzapine, and aripiprazole had stronger data supporting their use in treating behavioral and psychological symptoms of dementia compared with quetiapine (Tampi *et al.* 2016). Therefore, efficacy must be weighed against side effects when prescribing such antipsychotics in a patient with dementia.

Comparisons of antipsychotics versus benzodiazepines. Despite the high prevalence of benzodiazepine use for the treatment of behavioral complications in dementia, there is limited evidence to support the use of benzodiazepines for this purpose. Early studies that compared antipsychotics with benzodiazepines suffered from methodological flaws, particularly in sample selection and study design (Burgio *et al.* 1992; Stotsky 1984). A more recent meta-analysis of 18 clinical trials found limited clinical efficacy of benzodiazepine use in Alzheimer's disease, but such evidence is limited by a dearth of high-quality, controlled clinical trials (Defrancesco *et al.* 2015). Unfortunately, benzodiazepines are known to have deleterious effects on cognition in older adults, both with and without cognitive impairment (Lee *et al.* 2018; Pomara *et al.* 1991, 2015), and their use can lead to tolerance and dependence. Therefore, benzodiazepines should be used at low dosages, and use should be restricted to short-term crisis management of agitated and anxious behaviors if antipsychotics or other medications are ineffective.

Studies of Other Agents

A small-sample study by Tariot *et al.* (1998) suggested that carbamazepine was effective in the treatment of behavioral complications of Alzheimer's disease, and there were suggestions that valproate was efficacious in a single-site study by the same research group (Porsteinsson *et al.* 2001). However, there is insufficient evidence to support the use of valproic acid for behavioral complications of dementia (Liu and Wang 2020). A recent large meta-analysis (N = 889,378) observed that among older adults with dementia (mean age [?] 80 years), anticonvulsants were associated with an odds of death eight times higher than that of placebo (Watt *et al.* 2020). Nonetheless, anticonvulsants such as valproate are routinely prescribed in nursing homes.

In a 12-week placebo-controlled trial in patients with dementia and agitation, the SSRI citalopram showed a small but significant advantage over placebo in some but not all measures of efficacy (Porsteinsson *et al.* 2014). However, the majority of patients received citalopram at a dosage of 30 mg/day, which is higher than the FDA dosage limit of 20 mg/day, which was instituted because of QT prolongation on the electrocardiogram at higher dosages.

In a recent Phase II randomized double-blind, placebo-controlled discontinuation trial of 217 individuals with dementia-related psychosis who had a response to pimavanserin,

patients were observed to have a significantly lower risk of relapse with continuation of the drug than with discontinuation at 26 weeks (Tariot *et al.* 2021). Only 79 patients completed the trial because it was stopped early for efficacy; therefore, larger trials are needed to determine the effects of pimavanserin on dementia-related psychosis.

Studies of other medications, such as buspirone (Santa Cruz *et al.* 2017), trazodone (Sultzer *et al.* 1997), lithium (Devanand *et al.* 2017), and propranolol (Shankle *et al.* 1995), have involved case series or small samples. These medications can be considered as therapeutic options only after antipsychotic treatment has failed.

Use of Concomitant Psychotropics

Use of anticholinergic agents to treat EPS should be avoided, particularly in Alzheimer's disease, in which a cholinergic deficit is believed to underlie much of the cognitive impairment. Trazodone at dosages of 25-200 mg/day can be used as a hypnotic in these patients. Benzodiazepine use should be limited to short-term crisis management of anxiety or agitation, and sedative-hypnotics such as zolpidem should generally also be avoided.

Optimal Duration of Antipsychotic Treatment

A trial of 6-12 weeks usually is sufficient to determine the outcome of an antipsychotic treatment trial. If the optimal antipsychotic dosage is reached quickly, clinical response may occur within the first 1-2 weeks. On the other hand, the need to adjust the dosage because of side effects may require a relatively prolonged trial period. However, conflicting evidence exists regarding how long antipsychotic medications should be continued. Whereas some reports indicate a moderate to high rate of relapse after discontinuation (Avorn *et al.* 1992; Hortwitz *et al.* 1995), others suggest that antipsychotics and other psychotropics can be discontinued in nursing home patients with dementia without increased risk of behavioral symptom relapse.

In a large randomized double-blind study examining relapse risk after antipsychotic discontinuation (Devanand *et al.* 2012), 180 Alzheimer's disease patients with psychosis or agitation/aggression received 16 weeks of open treatment with risperidone (mean dosage = 0.97 mg/day). Responders were randomly assigned to receive continuation risperidone for 32 weeks, risperidone for 16 weeks followed by placebo for 16 weeks, or placebo for 32 weeks. In the first 16 weeks after randomization, patients who discontinued to placebo showed greater rates of relapse than those who were assigned to receive continuation risperidone, for a relapse rate of 60% for placebo versus 32.9% for continuation risperidone. During the second 16 weeks, relapse rates were again greater with discontinuation to placebo compared with continuation risperidone, for a relapse rate of 48.1% for placebo versus 15.4% for risperidone. In a planned post hoc analysis, it was observed that participants with severe hallucinations at baseline had a threefold higher likelihood of relapse compared with mild or no hallucinations. Such results suggest that if an antipsychotic is discontinued in an individual with severe psychotic symptoms such as hallucinations, the individual should be monitored closely for symptom recurrence (Patel *et al.* 2017).

In contrast, results from the Halting Antipsychotic use in Long-Term care (HALT) study of 139 nursing home residents revealed successful and sustainable reduction of antipsychotic use without symptom recurrence (Brodaty *et al.* 2018). A "deprescribing" intervention was established in which practitioners, pharmacists, and nurses were educated on nonpharmacological techniques for behavioral and psychological symptoms in dementia. Over the 12-month study, the number of older adults on regular antipsychotics was reduced by 81.7% without an associated increase in behavioral or psychological symptoms.

Based on the findings of Devanand *et al.* (2012) described above, it can be argued that if a patient has shown a clear response to antipsychotic treatment, that patient should be continued on treatment for several months (up to 8 months) if side effects are not prominent. However, because of the adverse effects of antipsychotics in dementia, many suggest that a discontinuation trial should be considered for patients whose symptoms have been significantly improved or have been in remission for 3-6 months (Steinberg and Lyketsos 2012).

Treatment Monitoring of Target Behavioral Symptoms

The heterogeneous nature of behavioral complications suggests that specific target symptoms should be identified before antipsychotic treatment is initiated, and then monitored serially during the course of treatment with a scale such as the NPI. Cognition and activities of daily living need to be monitored, preferably with brief instruments such as the Mini-Mental State Exam. In patients who are being maintained on antipsychotics for extended periods, assessment for TD using the Abnormal Involuntary Movement Scale should be conducted at regular intervals.

Antipsychotics in Other Neurocognitive Disorders in Older Adults

The relative efficacy of antipsychotics in dementia related to neurocognitive disorders other than Alzheimer's disease has not been studied extensively, although antipsychotic treatment trials that have included patients with vascular dementia and other forms of dementia did not reveal any differences in treatment response between diagnostic subtypes (De Deyn *et al.* 1999; Katz *et al.* 1999). With the exceptions of dementia with Lewy bodies and Parkinson's disease, in which EPS are likely to worsen with antipsychotics, the recommendations for the use of antipsychotics in Alzheimer's disease generally apply to their use in other types of dementia (i.e., vascular dementia and frontotemporal dementia.)

Dementia with Lewy bodies is a subtype of dementia characterized by prominent EPS, fluctuating clinical course, hallucinations, and extreme sensitivity to the neurological side effects of antipsychotics (McKeith 2006). Patients with Parkinson's disease who take the carbidopa-levodopa combination (Sinemet) or dopamine agonists can develop iatrogenic psychosis from these medications. Lowering the dosage of the dopaminergic agent can lead to remission of psychotic symptoms, but the price paid may be an unacceptable increase in parkinsonian symptoms (Breier *et al.* 2002b). In such cases, antipsychotics with a very low propensity to cause EPS (e.g., atypical antipsychotics) can be considered, although the optimal choice of antipsychotic is an open question. Although some analyses have observed olanzapine to be safe and effective (Cummings *et al.* 2002), others have found no advantage for olanzapine over placebo in these patients (Breier *et al.* 2002b). Clozapine may be of some value in patients with Parkinson's disease (Friedman and Fernandez 2002), but the need for specialized monitoring limits its utilization. Quetiapine use is generally well tolerated in these patients (Fernandez *et al.* 2002), but its efficacy is unclear in dementia with Lewy bodies. Pimavanserin, a selective inverse agonist at the serotonin 5-HT$_{2A}$ receptor, was approved by the FDA in 2016 and has been shown to be efficacious in treating psychosis in Parkinson's disease (Cummings *et al.* 2014), although it can be cost-prohibitive compared with other existing antipsychotics.

In patients with delirium, short-term antipsychotic use is a standard treatment strategy in clinical practice. Several analyses have found antipsychotics to be helpful in lowering delirium severity (Breitbart *et al.* 2002), but recent literature has called this into question. For example, a recent systematic review of 5,607 adult inpatients with delirium found no significant differences in delirium outcomes between haloperidol, second-generation antipsychotics, and placebo (Nikooie *et al.* 2019). Likewise, a recent double-blind randomized controlled trial of ICU patients with delirium and acute respiratory failure found no differences in delirium duration between haloperidol, ziprasidone, and placebo (Girard *et al.* 2018).

Therefore, cautious use of antipsychotics can be considered when nonpharmacological interventions have failed and symptoms are severe or dangerous. The choice of antipsychotic is often based on side-effect profile, as haloperidol has a low risk of anticholinergic effects, whereas quetiapine is highly sedating but is less likely to cause EPS.

Antipsychotics in Late-Life Schizophrenia

Most older adults with schizophrenia were first diagnosed as young adults, but a minority of patients are first diagnosed with schizophrenia later in life. Although age at onset may affect clinical presentation, it does not appreciably influence the likelihood of response to antipsychotics or the occurrence of side effects (Sable and Jeste 2002).

In elderly patients with schizophrenia, a thorough evaluation followed by treatment with low dosages of atypical antipsychotics is the optimal strategy. In general, atypical antipsychotics appear to be at least as efficacious as and better tolerated than typical antipsychotics in this population. In older patients with schizophrenia, switching from typical antipsychotics to risperidone has been reported to be effective and well tolerated (Barak *et al.* 2002).

It has been difficult to conduct placebo-controlled trials in older patients with schizophrenia because tapering and stopping antipsychotic medications in schizophrenia is associated with a high risk of relapse. In a 4-month comparison trial of flexible-dose risperidone (n = 175) versus quetiapine (n = 553) in 728 mixed-age patients with a variety of psychotic disorders, quetiapine was as effective as risperidone and was less likely to require adjustment of concomitant antiparkinsonian medication. However, quetiapine was associated with more sedation, dry mouth, and dizziness (Mullen *et al.* 2001).

Open-label quetiapine (mean dose = 137.5 mg) was evaluated in a 53-week study of 184 elderly patients (mean age = 76.1 years), 72% with Alzheimer's disease and 28% with other psychoses (mainly schizophrenia), and was found to be effective for psychotic symptoms (Tariot *et al.* 2000). Importantly, new-onset TD did not develop in any patient over the 1-year period. Although this study was limited by the lack of placebo control or comparison with another antipsychotic to establish efficacy, the relatively benign side-effect profile of quetiapine is noteworthy. However, the CATIE studies in patients with Alzheimer's disease suggested that quetiapine's lack of efficacy compared

with olanzapine and risperidone (quetiapine did not separate from placebo) should be an equally important consideration (Schneider *et al.* 2006).

The effectiveness of long-acting injectable antipsychotics (LAIs) in older adults was evaluated in a naturalistic study of 1,168 older adults with schizophrenia after discharge from hospitalization (Lin *et al.* 2020). In this study, 151 participants received an LAI prior to discharge and 1,017 participants were taking oral antipsychotics at time of discharge. Over the 1-year study period, individuals on LAIs had a significantly lower rehospitalization rate (53.6% for LAIs vs. 66.1% for oral antipsychotics) and a longer time to rehospitalization (257 days for LAIs vs. 115 days for oral antipsychotics). Although the NNT for prevention of rehospitalization was 8, the clinical utility LAIs in older adults could not be fully evaluated because there were no data on adverse events.

Antipsychotics in Other Disorders in Older Adults

Low-dose quetiapine is commonly used off-label for the treatment of insomnia in older adults. However, the small number of available studies examining quetiapine for insomnia are restricted to younger, healthy subjects (Cohrs *et al.* 2004; Tassniyom *et al.* 2010), and robust studies on the safety and efficacy of quetiapine for insomnia in older adults are lacking. In addition, older adults can be particularly sensitive to the cardiac, anticholinergic, cognitive, metabolic, and neurological (e.g., EPS) side effects. In general, quetiapine use for the treatment of insomnia in older adults is to be avoided.

MDD with psychosis is an uncommon but clinically important diagnosis in older individuals. Based on studies in mixed-age samples, antipsychotics combined with antidepressants are the pharmacological treatments of choice, but ECT is still considered the most effective treatment for this disorder (Mulsant *et al.* 2001b; Sackeim *et al.* 1995). Expert consensus guidelines suggest that antipsychotic medication should be continued for 6 months following treatment response in MDD with psychosis in older adults (Alexopoulos *et al.* 2001). A double-blind trial of combination pharmacotherapy for MDD with psychosis showed that treatment with olanzapine plus sertraline was superior to treatment with olanzapine plus placebo in both older and younger adult patients, a finding that highlights the importance of combination antipsychotic and antidepressant treatment (Meyers *et al.* 2009).

Antipsychotics are used widely in the treatment of the manic phase of bipolar disorder across the life span (Levine *et al.* 2000). In bipolar disorder, there is ample evidence for the efficacy of typical and atypical antipsychotics, both individually and in combination with mood stabilizers (Sachs *et al.* 2002; Tohen *et al.* 2002). However, there is a surprising lack of data on the use of antipsychotics in geriatric patients with bipolar disorder. Because lithium's toxicity, particularly in the neurological domain, is problematic in older adults, anticonvulsants and atypical antipsychotics are most frequently used to treat mania in this population. However, in the absence of controlled data, the optimal choice of antipsychotic and the optimal dosage to use in these patients are open questions that need to be answered in future research.

Conclusion

Clearly, antipsychotic medications, particularly atypical antipsychotics, have an important role to play in the treatment of psychosis and behavioral dyscontrol in Alzheimer's

disease, other types of dementia, and other neurodegenerative conditions. Antipsychotics remain the first-line treatment for schizophrenia and other psychotic disorders across the life span. When antipsychotic medications are used in elderly patients, monitoring of target symptoms, somatic side effects, potential drug interactions, cognition, and activities of daily living is necessary. Likewise, antidepressant medications remain the mainstay pharmacological treatment for late life depression. However, antidepressant medications have specific risks in older patients that should be reviewed by clinicians prior to prescribing these medications, and a risk-benefit analysis should always be considered.

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CHAPTER 62

Treatment of Women Excluding Pregnancy and Postpartum

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Reproductive-Related Events That Affect Psychiatric Disorders

Starting at puberty, females become more vulnerable to certain psychiatric disorders, a phenomenon that has been well documented (Bale and Epperson 2017). From menarche until menopause, females are approximately twice as likely as males to experience a major depressive disorder (MDD) episode (Bale and Epperson 2015), and the worldwide burden of disease due to MDD, as measured by disability-adjusted life years, is more than 1.5 times greater in females than in males (Cislaghi *et al.* 2020). Compared with males, females are at greater risk for panic disorder and onset of PTSD after exposure to an event that engenders a sense of helplessness, horror, or threat of death to self or others (Hantsoo and Epperson 2017). In addition to the greater burden of these disorders in females compared to males, the menstrual cycle, the perinatal period, and the menopause transition create unique psychiatric concerns. These periods of dynamic hormonal change are associated with increased risk for onset of mood disorders and cognitive changes, and these outcomes correlate with heightened distress (Bromberger and Epperson 2018; Epperson *et al.* 2013) and a decline in function (Epperson *et al.* 2015; Halbreich *et al.* 2003; Yang *et al.* 2008). Therefore, mood and cognitive complaints should be addressed by clinical providers who regularly treat women in their practice.

The aim of this chapter is to guide providers who prescribe neuroactive medications as pharmacotherapy specifically for postpubertal females experiencing psychiatric problems outside the perinatal period and common cognitive concerns in perimenopause and early postmenopause. The treatment of psychiatric illnesses during pregnancy and postpartum is covered in Chapter 63, "Psychopharmacology During Pregnancy and Lactation." Even though gonadal hormones have a broad impact on neurochemistry (McEwen and Parsons 1982), and sex differences have been observed in the pharmacokinetics (e.g., hepatic metabolism) of some psychotropic medications (Marazziti *et al.* 2013; Sramek *et al.* 2016), few studies have investigated whether sex affects the efficacy and tolerability of psychotropics (Duffy *et al.* 2020). Of those that have, the evidence generally does not suggest that pharmacotherapy for psychiatric problems should differ based on sex (except for those related to menstruation or menopause).

The first section of this chapter will indicate where sufficient evidence exists that would guide the prescriber to choose a class of medication or dosage differently for female versus male patients with the same disorder. The second section will recommend treatment options for menstrual cycle-related psychiatric concerns, focusing on treatment options for premenstrual dysphoric disorder (PMDD) and premenstrual exacerbation of psychiatric disorders. Because of the influences of sex hormones in these psychiatric concerns, drugs not typically considered in the context of psychopharmacology, such as steroid contraceptives and agonists or antagonists of the hypothalamic-pituitary-gonadal axis, that are effective in treating PMDD and premenstrual exacerbation will be described. The third section will consider treatment options for depression, psychosis, and cognitive complaints in perimenopausal and postmenopausal women as well as which psychotropics are safe to use in the context of chemical menopause. This section will also describe hormonal strategies as potential adjuncts to traditional psychopharmacology. In summary, this chapter focuses on the strength of the evidence for both psychotropic medications and other pharmacotherapies for psychiatric problems occurring in the context of hormonal changes outside the perinatal period and cognitive issues presenting during perimenopause and early postmenopause.

Sex Differences in the Safety and Efficacy of Psychotropic Medications

Antidepressants

Although the findings have been mixed, females may be more likely to respond to selective serotonin reuptake inhibitors (SSRIs) than males, whereas males may show a better response to serotonin-norepinephrine reuptake inhibitors (SNRIs) and the tricyclic antidepressant imipramine than females (Khan *et al.* 2005; Sramek *et al.* 2016). However, the magnitude of these differences may not be clinically significant, and SSRIs are still considered a first-line antidepressant for both sexes (Bayes and Parker 2018).

Antipsychotics

Although premenopausal females need lower dosages of antipsychotics to achieve efficacy, regardless of reproductive status, females are more likely to report side effects (Iversen *et al.* 2018; Lange *et al.* 2017; Seeman 2020). In a large naturalistic sample of patients taking antipsychotics for psychotic disorders, 13 side effects showed a sex difference, all of which were more frequently reported in females (Iversen *et al.* 2018) (Table 62-1). Females were also twice as likely as males to report the side-effect burden as being severe. To some extent, the greater side-effect burden may be explained by the fact that females are biologically more susceptible to certain adverse effects when taking antipsychotics. Not only does hyperprolactinemia occur more often in females (Melkersson *et al.* 2001), but high prolactin induced by antipsychotics reduces estrogen production, with unique effects in females (e.g., amenorrhea) (Iversen *et al.* 2018). Overall, females are more sensitive to antipsychotic-induced high prolactin and low estrogen, presenting with a host of symptoms driven by these hormonal changes, such as galactorrhea, infertility, hirsutism, sexual dysfunction, and decreased bone density (Iversen *et al.* 2018).

TABLE 62-1. Antipsychotic side effects reported more frequently in females than in males

* Concentration difficulties
* Sedation
* Accommodation disturbances (e.g., visual disturbances)
* Nausea
* Constipation
* Orthostatic dizziness
* Palpitations
* Pruritus
* Photosensitivity
* Increased pigmentation
* Weight loss
* Galactorrhea
* Headache

Source. Based on side effects reported in a large study of 834 patients with a psychotic disorder who were taking antipsychotics (Iversen *et al.* 2018).

Adjunctive estrogen treatment may be more effective in females than males (Begemann *et al.* 2012; Lange *et al.* 2017). A meta-analysis found that short-term estrogen treatment (for 2 to 8 weeks) was superior to placebo in augmenting the effect of antipsychotics, reducing total symptom severity and positive and negative symptoms in female patients with schizophrenia (Begemann *et al.* 2012). In a subanalysis of studies using estradiol products (either 17-b-estradiol or ethinyl estradiol), the effects were even stronger. In males with schizophrenia, estradiol valerate 2 mg/day (oral) treatment was not superior to placebo.

Because of safety concerns about long-term use of unopposed estrogens in women, combined oral contraceptives (COCs) are the first-line adjunctive therapy option for female patients of reproductive age whose symptoms are resistant to standard antipsychotic therapies (Begemann *et al.* 2012; Kulkarni *et al.* 2019). One review recommended use of COCs containing 17-b-estradiol, if possible, with at least 30 mcg of estrogen (Kulkarni *et al.* 2019). Despite promising case reports of adjunctive COCs improving psychosis (*N* = 2 [Coromina Sadurni *et al.* 2009; Felthous *et al.* 1980]), at least in the context of premenstrual exacerbation, no clinical trials have assessed the effect of COCs on symptom severity in women with schizophrenia. Importantly, the beneficial effects demonstrated in trials of estradiol cannot be extrapolated to formulations of combined estrogen and progestins, given that progestins could either increase or reduce the beneficial effect of estrogen. Despite the scarcity of randomized controlled trials (RCTs), COCs are nevertheless recommended because they are considered safe to use long-term, at least in studies in the general population (Hannaford 2000). Before starting the oral contraceptive pill, the psychiatric provider should confer with the patient's gynecologist.

Mood Stabilizers

For women needing a hormonal contraceptive agent and a mood stabilizer, drug interactions must be considered (Forrest *et al.* 2020). Hormonal contraceptive agents can interact with certain mood stabilizers, such as carbamazepine and oxcarbazepine, increasing clearance of hormones in COCs, transdermal patches, progestogen-only pills, and progestogen implants (Miller *et al.* 2015). Such interactions jeopardize the efficacy of the hormonal contraceptive in protecting women from unintended pregnancy. Some providers prescribe higher-dose contraceptives, but no research has been conducted to confirm the dosage that is needed to provide adequate contraception. Alternative birth control methods should be considered, including copper intrauterine devices (IUDs), levonorgestrel-releasing intrauterine systems, depot medroxyprogesterone acetate injections, and barrier methods. Similarly, estrogen-based contraceptives can compromise the efficacy of certain mood stabilizers (valproate and lamotrigine) by increasing their clearance and thereby lowering their circulating levels (Forrest *et al.* 2020). The progesterone-containing IUD is a highly reliable contraceptive with fewer effects on drug metabolism. Given the potential for valproate to increase the risk of fetal anomalies, reproductive-age women should avoid using it when possible. If valproate is necessary due to lack of efficacy of other mood stabilizing medications, a reliable method of birth control should be used.

Treating Menstrual Cycle-Related Psychiatric Concerns

Premenstrual Dysphoric Disorder

PMDD presents as a combination of emotional (e.g., depressed mood, anxiety, irritability, anger), behavioral (e.g., overeating, lethargy, insomnia), and physical (e.g., breast tenderness, weight gain) symptoms that cause significant distress and functional impairment (Epperson *et al.* 2012; Maharaj and Trevino 2015). This disorder is exceptionally common, with 1.8%-5.8% of menstruating women experiencing PMDD within a 12-month period (American Psychiatric Association 2013). The burden of this disorder is substantial: women with PMDD show impaired functioning across various domains (Halbreich *et al.* 2003; Yang *et al.* 2008) and are at a substantially higher risk for suicidal ideation, plans, and attempts (Osborn *et al.* 2021).

The diagnostic criteria in DSM-5 (American Psychiatric Association 2013) require that at least 5 out of 11 specific symptoms occur in most menstrual cycles, that symptoms present in the final week of the cycle, and that they improve within a few days of menses onset. A presumed diagnosis of PMDD must be confirmed with at least 2 months of prospective daily ratings of symptoms on a standardized daily questionnaire, such as the Daily Record of Severity of Problems (Endicott *et al.* 2006) or the Carolina Premenstrual Assessment Scoring System (Eisenlohr-Moul *et al.* 2017b). To make a PMDD diagnosis, it is critical to confirm that symptoms are isolated to the luteal phase and resolve within the first few days of menstruation. This differentiates PMDD from premenstrual exacerbation of an ongoing psychiatric illness, a topic discussed later in this section.

Although psychological symptoms are necessary for a PMDD diagnosis, the wide range of psychological, behavioral, and physical symptoms that occur in women with PMDD can make treating the disorder complex. Multiple pharmacological interventions may be needed to alleviate all burdensome symptoms. In addition, changes in terminology and diagnostic criteria have meant that samples of patients in research studies across the decades have been particularly heterogeneous. Because PMDD did not gain status as an official diagnosis until 2013, when DSM-5 was published, studies conducted before that often refer to participants as having premenstrual syndrome (PMS). Currently, PMS is used to describe menstrual-related mood or physical symptoms that interfere with daily life but do not meet criteria for a PMDD diagnosis. Before PMDD became an official diagnosis, however, many studies recruited women with a symptom severity and timing of onset consistent with DSM-5 criteria for PMDD even though they are referred to as having PMS. Recommendations for pharmacotherapies included in this section can be considered for those with severe PMS as well as PMDD.

Serotonin Reuptake Inhibitors

RCTs have consistently found that antidepressants with stronger serotonergic activity are superior in treating PMDD and mood symptoms of PMS than those with weaker serotonergic effects (Eriksson *et al.* 1995; Freeman *et al.* 1999; Pearlstein *et al.* 1997). As a result, the SSRIs sertraline

(50-150 mg/day), fluoxetine (10-20 mg/day), citalopram (10-30 mg/day), and escitalopram (10-20 mg/day) are considered the gold standard option for treating PMDD and severe PMS (Maharaj and Trevino 2015; Shah *et al.* 2008). Although paroxetine (12.5-25 mg/day) is an SSRI that effectively treats PMDD, it is nevertheless considered a second-line option for reproductive-age women because of concerns that it may increase the risk of congenital cardiac defects (Bar-Oz *et al.* 2007). The tricyclic antidepressant clomipramine (25-75 mg/day) and the SNRIs venlafaxine (50-200 mg/day) and duloxetine (60 mg/day) are also second-line treatment options (Maharaj and Trevino 2015). The SNRI venlafaxine is associated with worse discontinuation symptoms than SSRIs, and clomipramine has burdensome side effects, such as sedation, dry mouth, and weight gain (Sundblad *et al.* 1992, 1993). Except for duloxetine, which has been studied only with continuous dosing (Mazza *et al.* 2008; Ramos *et al.* 2009), all have demonstrated efficacy when dosed either continuously (administered daily throughout the entire menstrual cycle) or during the luteal phase only (administered in the 2 weeks before menses onset, also called intermittent dosing) (Maharaj and Trevino 2015).

Few studies provide evidence-based guidance for prescribers on whether to use luteal phase or continuous administration. A Cochrane Review of RCTs compared the efficacy of luteal phase dosing and continuous dosing of SSRIs in treating PMS and PMDD (Marjoribanks *et al.* 2013). These dosing regimens were found to be equally effective (Marjoribanks *et al.* 2013). Although this conclusion differed from that of a previous meta-analysis showing that continuous dosing was superior to luteal phase dosing (Shah *et al.* 2008), methodological differences account for this discrepancy. The methods of Marjoribanks *et al.* (2013) were stronger, leading to more convincing conclusions. Only a few studies have conducted a head-to-head comparison of these dosing regimens within the same study, but of those that have, luteal phase dosing was found to be at least as effective as continuous phase dosing (Freeman *et al.* 2004a; Landen *et al.* 2007; Steiner *et al.* 1997; Wikander *et al.* 1998; Wu *et al.* 2008). However, these dosing regimens may offer a trade-off in terms of efficacy (for alleviating certain symptoms) and tolerability (for inducing certain side effects). In an RCT, continuous dosing of paroxetine was more effective in treating some symptoms (e.g., depressed mood) but also increased the occurrence of an adverse effect (decreased libido) (Landen *et al.* 2007). In another study, overall side effects were more common in participants receiving continuous dosing than in those receiving luteal phase dosing, and in particular, headaches were reported more often when dosing was continuous (Steiner *et al.* 1997).

Another potential dosing regimen is symptom-onset dosing, in which medication is administered at the start of PMDD/PMS symptoms through the first few days of menstrual bleeding. Symptom-onset dosing has not been studied to the same extent as luteal phase and continuous dosing. In two RCTs, the efficacy of symptom-onset dosing was only modestly better than placebo (Yonkers *et al.* 2006, 2015), with another RCT suggesting that women with more severe PMDD may respond better to luteal phase dosing than to symptom-onset dosing (Freeman *et al.* 2005). At this time, symptom-onset dosing is not generally recommended, although it is not contraindicated if the patient is responsive to treatment and trying to limit side effects.

If symptoms are present at low levels during much of the follicular phase or symptom onset is unpredictable (e.g., if a woman has irregular menstrual cycles), then continuous administration is recommended. Furthermore, if physical symptoms are severe, some evidence suggests that continuous dosing may be more effective than luteal phase dosing (Marjoribanks *et al.* 2013). If symptoms are present during the luteal phase only and the onset of symptoms is predictable (e.g., if a woman has regular menstrual cycles), then luteal phase dosing could be an appropriate option, with the advantages of lower financial cost and fewer side effects (e.g., sexual dysfunction may be reduced). For some women, higher dosages of SSRIs are needed to adequately treat physical symptoms when luteal phase dosing is used (Cohen *et al.* 2002; Miner *et al.* 2002). Other treatment options include increasing the dosage during the luteal phase rather than using the same dosage throughout the cycle (called semi-intermittent dosing) or starting the medication only at the onset of symptoms (Steiner *et al.* 2006). Treating during the luteal phase only or at symptom onset is possible because the onset of action of SSRIs and other serotonin reuptake inhibitors (SRIs) is much more rapid when used for PMDD than when used for depression and anxiety disorders. In fact, one study found that the SSRI fluoxetine improved premenstrual symptoms on the second day of administration (Steinberg *et al.* 2012). Thus, deciding on a dosing regimen involves considering the predictability and duration of symptoms and weighing the potential improvement of specific symptoms against increased risk of side effects.

Combined Oral Contraceptives

Given that oral contraceptive pills replace fluctuating levels of endogenous ovarian steroids with more stable levels of exogenous hormones, they have been tested for their effectiveness in treating PMDD. A recent meta-analysis found that although COCs (estrogens plus progestins) are moderately effective at treating overall premenstrual symptoms, they are no more effective than placebo in treating premenstrual depressive symptoms (de Wit *et al.* 2021). Furthermore, even though the formulation of drospirenone (3 mg) combined with ethinyl estradiol (20 mcg) dosed as 24 days of hormone pills followed by 4 days of inactive pills (24/4 days) received FDA approval for the treatment of PMDD (U.S. Food and Drug Administration 2011) and is considered a second-line treatment option for PMDD and PMS (Maharaj and Trevino 2015), this formulation has not demonstrated superiority over other COCs in treating premenstrual depressive symptoms specifically (de Wit *et al.* 2021).

RCTs that have tested which regimen of drospirenone/ethinyl estradiol is most effective show mixed results. One randomized open-label study found that continuous dosing of drospirenone (3 mg) combined with ethinyl estradiol (20 mcg) for 168 days without a hormone-free interval was noninferior to the 24/4 day cyclical regimen (Machado *et al.* 2017). A double-blind, placebo-controlled RCT tested the efficacy of intermittent (21/7) versus continuous dosing of drospirenone (3 mg)/ethinyl estradiol (20 mcg) in treating premenstrual dysphoria but found neither regimen to be better than the other or superior to placebo (Eisenlohr-Moul *et al.* 2017a).

However, this finding contrasts with results from a double-blind, placebo-controlled RCT, which showed that drospirenone (3 mg)/ethinyl estradiol (30 mcg) in a 21/7 regimen reduced PMS severity compared with placebo (Shehata *et al.* 2020). Thus, currently, the most effective dosing schedule for drospirenone-containing COCs remains unknown until further investigation.

For women seeking treatment for overall premenstrual symptoms and not premenstrual depressive symptoms specifically, the formulation drospirenone (3 mg) combined with ethinyl estradiol (20 mcg) may be a good choice, especially if they are also seeking contraception. However, prescribing physicians should be aware that drospirenone-containing birth control pills may be associated with as much as a threefold higher risk for blood clots than products containing levonorgestrel or another type of progestin, but that the absolute risk of blood clots in women using COCs (overall) is still low (3 to 9 out of 10,000 per year) relative to the 1 to 5 women out of 10,000 each year who experience blood clots who are not taking COCs (U.S. Food and Drug Administration 2012).

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone (GnRH) agonists reliably decrease ovarian hormone production (after a brief initial increase). This results in anovulation and amenorrhea, with GnRH agonists essentially creating a chemically induced menopausal state. Multiple studies show that GnRH agonists at dosages that suppress ovulation are effective in mitigating both physical and mood symptoms (Wyatt *et al.* 2004);

however, they are not considered a first-line option for PMDD or severe PMS because they create a hypogonadal state, inducing burdensome side effects (Maharaj and Trevino 2015). Besides having an unfavorable side-effect profile, they are also costly.

Three treatment options have been evaluated: leuprolide (3.75 mg intramuscular injection monthly), goserelin (3.6 mg subcutaneous injection monthly), and histrelin (one annual subcutaneous implant with 50 mg/implant). A meta-analysis of five RCTs testing the efficacy of treating PMS or PMDD with GnRH agonists found that both physical and mood symptoms improved more with GnRH agonists than with placebo (Wyatt *et al.* 2004). Although the effect was observably stronger for physical symptoms (e.g., breast tenderness, weight gain) than mood symptoms (e.g., depression, irritability), the difference was not statistically significant.

Treatment with GnRH agonists should be limited to 6 months unless add-back estrogen and progesterone are also administered. Otherwise, GnRH agonists can cause menopause-like side effects (e.g., decreased bone mineral density, hot flashes, night sweats) and masculinization (Maharaj and Trevino 2015). Although there is concern that add-back hormone therapy will lead to a resurgence of premenstrual symptoms, in the previously referenced meta-analysis, three studies that used add-back hormone therapy did not decrease the efficacy of GnRH agonists significantly (Wyatt *et al.* 2004).

One small randomized, double-blind crossover trial of patients receiving GnRH agonist monotherapy (leuprolide) tested different add-back hormone formulations to determine which was most beneficial in terms of mood effects (Segebladh *et al.* 2009). Three add-back combinations were studied: 1.5 mg gel estradiol/400 mg progesterone, 1.5 mg gel estradiol/placebo, and 0.5 mg gel estradiol/400 mg progesterone. The 1.5 mg gel estradiol/placebo combination was the best add-back option for patients with PMDD, as it was associated with lower irritability and depression compared with GnRH agonist monotherapy. However, estradiol-only treatment is not considered a safe option for women with an intact uterus because it can cause endometrial hyperplasia. The group that received 1.5 mg gel estradiol combined with progesterone had a resurgence of premenstrual symptoms that was more pronounced than in the group receiving 0.5 mg gel estradiol with progesterone. The 0.5 mg gel estradiol/progesterone group did not differ from the group receiving GnRH agonist monotherapy on measures of irritability, anxiety, depression, and impact on daily life but did report significantly more bloating. Overall, these findings are in line with previous research showing that when estradiol is combined with progestogens or natural progesterone, a higher dosage of estradiol causes more premenstrual symptoms than a lower dosage of estradiol (Bjorn *et al.* 2003).

Tibolone, a synthetic compound with estrogenic, androgenic, and progestogenic properties, has shown initial efficacy as a hormone therapy option in women with severe PMS who are using GnRH agonists. In a small RCT, tibolone outperformed placebo in reducing the number of hot flashes per day without exacerbating physical or psychological premenstrual symptoms (Di Carlo *et al.* 2001). Despite showing initial promise, in the past two decades since that RCT was published, no additional RCTs have followed up on these findings in women with PMS or PMDD. Although research supports the efficacy of various agents as add-back therapies, limited evidence precludes a strong recommendation of one type of add-back therapy over another (McLaren *et al.* 2012). Prescribers may need to try several add-back strategies to minimize resurgence of PMDD or PMS symptoms. Given the financial cost, menopause-like side effects, and lack of long-term safety data, prescribers should consider GnRH agonist treatment only for those with severe symptoms after SSRIs, SNRIs, and COCs have been given an adequate trial.

Serotonin Type 1A Receptor Agonist

Buspirone (10-40 mg/day), a partial serotonin type 1A receptor agonist, has shown efficacy in treating PMS and PMDD in two RCTs and is considered a second-line treatment option (Maharaj and Trevino 2015). A double-blind, placebo-controlled RCT tested the efficacy of luteal phase dosing versus continuous dosing of buspirone, ranging from 10 to 40 mg/day depending on response and tolerability (Landen *et al.* 2001). Although both dosing schedules observably improved all four mood symptoms (irritability, depressed mood, affect lability, and tension), only continuous dosing of buspirone was significantly more effective than placebo in treating irritability. A single-blind RCT compared buspirone 10 mg/day and fluoxetine 20 mg/day (both dosed continuously) in treating women diagnosed with PMS on the basis of changes in negative mood across three consecutive menstrual cycles (Nazari *et al.* 2013). Both medications demonstrated significant efficacy in the treatment of PMS, with neither showing superiority. Buspirone has a slow onset of action and has the unwanted side effects of sedation and cognitive and psychomotor impairment (Maharaj and Trevino 2015). In general, buspirone is well tolerated and may be a good alternative for patients who experience sexual dysfunction on SRIs. However, large double-blind, placebo-controlled trials are needed to investigate the efficacy, dosing, and side effects of buspirone further.

GABA Agonist

Alprazolam (0.25-0.75 mg/day), a benzodiazepine dosed from the luteal phase into menses, is not considered a first-line treatment for PMS or PMDD because of its lower efficacy rate compared with SSRIs (e.g., Diegoli *et al.* 1998) and the potential for benzodiazepine abuse (Maharaj and Trevino 2015). Six double-blind, placebo-controlled, randomized trials have been conducted (four crossover trials: Berger and Presser 1994; Harrison *et al.* 1990; Schmidt *et al.* 1993; Smith *et al.* 1987; two parallel-arm trials: Diegoli *et al.* 1998; Freeman *et al.* 1995). Although one study showed no benefit from alprazolam relative to placebo except for a statistically but not clinically significant improvement in depressive symptoms (Schmidt *et al.* 1993), in all other studies alprazolam was superior to placebo, improving a wide range of symptoms, including anxiety, irritability, tension, and depression (Berger and Presser 1994; Diegoli *et al.* 1998; Freeman *et al.* 1995; Harrison *et al.* 1990; Smith *et al.* 1987). However, alprazolam can induce sedation and impair cognitive and psychomotor functioning, particularly at higher dosages (Verster and Volkerts 2004). When the dosage was tapered with the onset of menses, no clinically significant withdrawal symptoms were observed (Freeman *et al.* 1995).

Dopamine Agonists

Luteal phase administration of the dopamine agonist bromocriptine (2.5-7.5 mg/day) was shown to decrease premenstrual mastalgia in women with

PMS (Elsner *et al.* 1980; Meden-Vrtovec and Vujic 1992; Ylostalo *et al.* 1982), perhaps because of its

prolactin-reducing properties. A review indicated that bromocriptine has inconsistent efficacy for other premenstrual symptoms (Halbreich *et al.* 2006). In a randomized, open-label trial comparing bromocriptine (dosed at 5 mg daily in the second half of the cycle) to cabergoline (dosed at 0.5 mg weekly in the second half of the cycle) (Aydin *et al.* 2010), cabergoline, a newer dopamine agonist, showed efficacy similar to that of bromocriptine in treating premenstrual mastalgia but fewer side effects such as nausea, vomiting, and headaches. Based on the current evidence, bromocriptine or the newer cabergoline may be helpful as an adjunct to first-line agents for women with PMDD who experience particularly bothersome mastalgia.

Aldosterone Antagonist

Luteal phase dosing of spironolactone (50-100 mg/day) is another strategy for treating bloating and mastalgia associated with PMDD and PMS (Maharaj and Trevino 2015). However, its effects on mood and other physical symptoms related to PMDD and PMS remain unclear, and findings are rather mixed (Halbreich *et al.* 2006). When treated with spironolactone, patients need to be monitored periodically for hyperkalemia.

Synthetic Hormones

Danazol is a synthetic androgen with some antiestrogen effects. At dosages greater than 200 mg/day, danazol suppresses ovulation, which drives its beneficial effects (Halbreich *et al.* 1991). Across multiple double-blind, placebo-controlled, randomized trials, danazol improves premenstrual mood and physical symptoms, particularly mastalgia (Deeny *et al.* 1991; Gilmore *et al.* 1985, 1989; Hahn *et al.* 1995; Kontostolis *et al.* 1997; Watts *et al.* 1987). However, its side effects include weight gain, hirsutism, acne, and decreased high-density lipoprotein cholesterol. One RCT tried dosing 200 mg/day of danazol in the luteal phase only (O'Brien and Abukhalil 1999). This regimen does not suppress ovulation, which is critical to the symptom relief of danazol (Halbreich *et al.* 1991), so although fewer side effects occurred, the only symptom alleviated was mastalgia (O'Brien and Abukhalil 1999). Overall, danazol is as efficacious as GnRH agonists but has more adverse effects and long-term risks (Halbreich *et al.* 2006), so its use in treating PMS and PMDD may be limited.

Summary: Treatment of Premenstrual Dysphoric Disorder

In summary, SSRIs have the best evidence for efficacy and are the first-line treatment for PMDD and premenstrual dysphoria in those with moderate to severe PMS. As with the treatment of other mood disorders, it is prudent to try several different serotonergic antidepressants, using continuous daily dosing if luteal dosing is not effective, before assuming that antidepressants are not effective for a given patient. Given the rapid onset of action of these drugs in the treatment of PMDD and PMS, a beneficial effect is expected in the first cycle. If the response is suboptimal, then a different dosage, regimen (e.g., luteal phase dosing or continuous dosing), or medication can be tried during the next menstrual cycle. However, approximately 40% of women with PMDD or PMS do not respond to SSRIs (Halbreich 2008), and SRIs are less effective for treating the physical symptoms of PMDD than the mood symptoms.

For those with PMDD or PMS who need contraception, there is evidence that some COCs can exacerbate PMDD and PMS mood symptoms even if they improve physical symptoms (Skovlund *et al.* 2016). If PMDD is suspected in a patient seeking contraception, it would be prudent to use either a drospirenone-containing COC or an IUD (at least to not exacerbate mood symptoms), although other methods are not contraindicated for women with PMDD or severe PMS. Psychiatrists and psychiatric nurse practitioners with little knowledge of contraception methods should collaborate with the patient's gynecologist or primary care provider. Drospirenone-containing COCs are effective in the treatment of overall premenstrual symptoms for patients with PMDD even though they are not more efficacious than placebo in treating depressive symptoms specifically.

For women with severe PMDD who are not sufficiently responsive to or cannot tolerate serotonergic antidepressants or drospirenone-containing COCs, GnRH agonist treatment should be considered, particularly for women with suicidal ideation or severe functional impairment. GnRH agonists can provide much-needed relief for these women while their providers determine an add-back strategy that does not exacerbate PMDD symptoms. GnRH therapy must be initiated in consultation and collaboration with the patient's gynecologist or primary care provider.

Premenstrual Exacerbation of Psychiatric Disorders

Premenstrual exacerbation (PME) is defined as premenstrual worsening of a preexisting psychiatric disorder (Hsiao *et al.* 2004) and is exceptionally common among women and girls with psychiatric disorders (58% of women and girls with a depressive disorder [Hartlage *et al.* 2004]; 44%-66% of women with bipolar disorder in prospective studies [Teatero *et al.* 2014]; 35%-45% of women with social anxiety disorder in a retrospective study [van Veen *et al.* 2009]; 20%-32% of women with psychotic disorders [Reilly *et al.* 2020]). Many women already taking psychotropic mediations still experience PME of their psychiatric symptoms (e.g., Hartlage *et al.* 2004), suggesting that their illness is not being adequately managed with current dosing regimens. For example, women taking antidepressants do not differ on the number of symptoms that become worse in the premenstrual phase compared to those not taking antidepressants (Hartlage *et al.* 2004). Even among women who appeared to be effectively treated with their current medication regimen (i.e., were not currently depressed based on semistructured diagnostic interviews), 44% nevertheless experienced PME of at least one symptom (Hartlage *et al.* 2004). In part, current dosing regimens, which typically involve a fixed dosage of medication across the menstrual cycle, may be inadequate because menstrual cycle hormonal changes affect the absorption, distribution, metabolism, and excretion of many drugs (Soldin *et al.* 2011). In fact, many small studies have shown that the blood levels of psychiatric mediations decrease substantially from the follicular phase to the luteal phase of the menstrual cycle despite constant dosages (e.g., Conrad and Hamilton 1986; Kimmel *et al.* 1992).

Despite the prevalence of PME, almost no clinical trials have tested which treatment options alleviate PME of psychiatric symptoms. Currently, treatment recommendations are extrapolated from case reports and treatment regimens used for PMS and PMDD (e.g., semi-intermittent dosing, in which medication dosage is increased during the luteal phase of the menstrual cycle) (Leahy 2017). The importance of considering PME among menstruating female patients cannot be overstated. Physicians who ignore the menstrual cycle risk simultaneously undertreating and overtreating their patients and potentially misinterpreting cycle-dependent symptoms as the medication being ineffective or causing side effects. Furthermore, many women who seek treatment for PMS or PMDD actually have PME of a psychiatric disorder. For example, as many as half of women seeking treatment for premenstrual disorders have PME of a depressive disorder (Plouffe *et al.* 1993). Therefore, careful consideration is needed regarding which symptoms occur at which phases of the menstrual cycle and whether women already on a psychiatric medication are experiencing breakthrough symptoms. Physicians should have women record daily premenstrual symptoms for at least 2 months to differentiate between PMDD and PME (Eisenlohr-Moul *et al.* 2017b; Endicott *et al.* 2006).

Major Depressive Disorder

Two small RCTs tested the efficacy of oral contraceptive pill (drospirenone/ethinyl estradiol) augmentation of antidepressants in preventing premenstrual breakthrough depression but found mixed results (Joffe *et al.* 2007; Peters *et al.* 2017). A pilot study of women who had persistent PME of depression on a constant dosage of sertraline were entered into a double-blind, placebo-controlled crossover trial to assess whether increasing the dosage of sertraline during the luteal phase worked better than increasing the dosage across the entire menstrual cycle (Miller *et* *al.* 2008). Semi-intermittent dosing resolved PME of depression, such that depression scores no longer differed in the luteal and follicular phases of the menstrual cycle, a difference that remained in the placebo group. This regimen has been used successfully in previous cases (Jensvold *et al.* 1992; Kimmel *et al.* 1992; Miller *et al.* 2002). Taken together, this evidence supports the use of dosage increases during the luteal phase rather than fixed dosage increases across the menstrual cycle.

Bipolar Disorder

According to a study following premenopausal women with bipolar disorder for 1 year, women with PME of bipolar disorder have greater overall symptom severity and increased risk of relapse in comparison with women with bipolar disorder without PME (Dias *et al.* 2011), demonstrating the need to adequately treat these women. Women with PME of bipolar disorder may benefit from variable dosing (Miller and Miller 2001). For example, in one case report, increasing the dosage of lithium for the week before expected menses onset was effective in reducing breakthrough affective psychosis symptoms in a patient with bipolar disorder mixed with psychotic features (Conrad and Hamilton 1986). Despite the importance of effectively managing bipolar disorder across the menstrual cycle, no treatment regimens for PME of bipolar disorder have been studied in clinical trials. Furthermore, distinguishing between bipolar disorder and PMDD or PMS is a diagnostic challenge with important implications, given that prescribing antidepressants to women with bipolar disorder can increase the risk of mania and hypomania (Miller and Miller 2001). In addition, bipolar disorder and PMDD are highly comorbid (Cirillo *et al.* 2012), so in the case of comorbidity, physicians need to be aware of the comorbid bipolar disorder in order to choose an appropriate treatment (Sepede *et al.* 2020).

Anxiety Disorders and Trauma-and Stressor-Related Disorders

Findings from prospective studies are mixed regarding the frequency of PME among women with an anxiety disorder or trauma-related disorder, such as PTSD (Nillni et al. 2021). One recent review concluded that there is not a universal at-risk menstrual cycle phase for women with an anxiety disorder or PTSD (Nillni *et al.* 2021). Thus, there are insufficient data to recommend changes in treatment regimen across the menstrual cycle due to PME of anxiety disorders or PTSD.

Schizophrenia

For PME of schizophrenia, physicians must decide on a case-by-case basis whether to raise antipsychotic dosages during the premenstrual phase, add hormone therapy (e.g., estrogens, estrogen/progesterone combinations), or target PMDD symptoms (Seeman 2012a). A case report found that two of four chronic inpatients with a diagnosis of schizophrenia or schizoaffective disorder showed improvement of their premenstrually exacerbated symptoms with daily oral conjugated estrogen (Premarin 0.625 mg) administered continuously for 3 months (Liao *et al.* 2002). A double-blind, placebo-controlled RCT in reproductive-age women with schizophrenia found that the addition of a 100-mcg estradiol transdermal patch produced significantly greater reductions in positive symptoms and general psychopathology symptoms relative to treatment with antipsychotic medication alone (Kulkarni *et al.* 2008). However, this study was not specific to women with PME, and more research is needed to determine which dosage, duration, and type of estrogen is most efficacious in treating premenstrual breakthrough symptoms.

Currently, treatment with estrogen remains controversial and has not been FDA approved for treating PME of schizophrenia (Seeman 2012a). However, low-dose birth control pills are a safe initial intervention for women with no contraindications (e.g., history of thromboembolic events). In a report of one patient with premenstrual psychosis, the oral contraceptive pill prevented the recurrence of psychotic symptoms in the premenstrual phase of the cycle (Coromina Sadurni *et al.* 2009). This may be because estrogen and progesterone administered orally interact with metabolizing enzymes and may boost blood levels of certain antipsychotics, which may be helpful for PME of psychotic symptoms (e.g., Chetty and Miller 2001; Gabbay *et al.* 2002).

Other treatment options include adding SSRIs if the premenstrually exacerbated symptoms are anxiety and depression or boosting the dosage of a prolactin-sparing antipsychotic for 3-5 days before menstruation if the exacerbated symptoms involve psychosis (Seeman 2012a). Case reports of women with PME of schizophrenia have indicated that adding the long-acting hormonal agent medroxyprogesterone acetate (Levitte 1997) or lithium (Glick and Stewart 1980) to antipsychotic treatment was efficacious when psychotic symptoms were exacerbated in the luteal phase of the cycle.

Summary: Treatment of Premenstrual Exacerbation of Psychiatric Disorders

In summary, PME of ongoing psychiatric disorders has been reported. However, few prospective RCTs have examined the effectiveness of pharmacological manipulations in treating breakthrough symptoms. Based on the current literature, it is reasonable to try increasing the antidepressant dosage during the luteal phase for women with confirmed PME of MDD. To manage PME in bipolar disorder or schizophrenia, luteal phase increase of a daily medication or addition of a new medication can be considered on a case-by-case basis with careful monitoring of the risks and benefits.

Treating Psychiatric Concerns in the Context of the Menopause Transition

The menopause transition is associated with fluctuating levels of ovarian hormones (e.g., estradiol) that can lead to a wide range of physical (e.g., vasomotor), behavioral (e.g., insomnia), and psychiatric (e.g., depression, anxiety) symptoms (Gordon *et al.* 2016, 2019), some of which may overlap with psychiatric disorders (Soares and Taylor 2007). For example, low energy, poor concentration, sleep problems, weight gain, and libido decreases are symptoms that occur in perimenopause and early postmenopause and in common psychiatric disorders, such as MDD (Soares and Taylor 2007). Selection of pharmacotherapy should consider whether a given medication is likely to exacerbate symptoms that co-occur with perimenopause and postmenopause (e.g., sexual dysfunction, weight gain) and whether it interacts with other drugs commonly used during the menopause transition, especially given the likelihood of concomitant use of other medications at this life stage (Maki *et al.* 2018).

Table 62-2 summarizes the reproductive phases as defined in the revised Stages of Reproductive Aging Workshop (STRAW+ 10) staging system (Harlow *et al.* 2012). Onset of vasomotor symptoms (VMS), depression, anxiety, and sleep and cognitive complaints can occur in perimenopause, when women may not be aware of menstrual irregularity yet (Gracia and Freeman 2018; Huang *et al.* 2018; Woods and Mitchell 2005). It is critical that mental health care providers familiarize themselves with this epidemiology because their patients are likely to report some, if not all, of these changes. Moreover, new onset of MDD is common during perimenopause (Cohen *et al.* 2006; Freeman *et al.* 2006), although MDD with perimenopause onset usually resolves within 2 years of the final menstrual period (Freeman *et al.* 2014). Therefore, treatment of new-onset MDD may not necessitate long-term therapy, although those who have a history of MDD before onset of the menopause transition may have ongoing concerns for years past the final menstrual period. Moreover, adverse childhood experiences increase the risk of new-onset MDD during perimenopause as well as the likelihood of experiencing MDD across the lifetime (Epperson *et al.* 2017). A prior history of MDD, a positive smoking history, and Black race are associated with earlier onset of menopause (Bromberger *et al.* 1997; Harlow *et al.* 2003; D. Zhu *et al.* 2018), and this should be considered when a woman presents with new-onset psychiatric concerns.

TABLE 62-2. Menstrual cycle characteristics of reproductive stages

Stage	Menstrual cycle characteristics

Stage	**Menstrual cycle characteristics**
Reproductive	
Early	Variable to regular
Peak	Regular
Late	Regular or subtle changes in flow heaviness or cycle length
Perimenopause	
Early	Increase or decrease in cycle length of [?] 7 days for at least one cycle in the past year
Late	Interval of amenorrhea ([?] 60 days)
Postmenopause	
--	Begins 12 months after the final menstrual period

Source. Based on the Revised Stages of Reproductive Aging Workshop (STRAW + 10) staging system for reproductive aging in women (Harlow *et al.* 2012).

Major Depressive Disorder

As described, perimenopause is a period of vulnerability for the development of depressive symptoms and major depressive episodes. Women with a history of depression were almost five times more likely to be diagnosed with MDD in the menopause transition than women without this history (Freeman *et al.* 2004b). In two longitudinal studies, premenopausal women with no prior history were two to four times more likely to report depressed mood in the menopausal transition compared to the premenopausal stage (Cohen *et al.* 2006; Freeman *et al.* 2006).

Dramatic changes in hormones during the menopause transition contribute to depression, as evidenced by research showing correlations between hormonal variability (in estradiol, follicle-stimulating hormone, and luteinizing hormone) and depressed mood (Freeman *et al.* 2004b, 2006; Ryan *et al.* 2009). Depression during perimenopause typically presents with classic depressive symptoms in combination with typical menopausal symptoms (e.g., VMS, sleep disturbance, weight changes, sexual concerns, and problems with memory and concentration) (Maki *et al.* 2018). As mentioned previously, menopausal symptoms often overlap with depressive symptoms (Soares and Taylor 2007), which can make diagnosing depression more challenging. This section draws extensively from the guidelines for treating perimenopausal depression published by experts from the North American Menopause Society (NAMS) and the Women and Mood Disorders Task Group of the National Network of Depression Centers (Maki *et al.* 2018, 2019). Psychiatrists and psychiatric nurse practitioners who regularly prescribe to midlife women may benefit from the Menopause Practitioner course offered by NAMS.

Antidepressants

Antidepressants are the first-line pharmacotherapy choice for treating perimenopausal and postmenopausal depression. Data on efficacy and tolerability support the use of SSRIs and SNRIs (Maki *et al.* 2018). However, only the SNRI desvenlafaxine has been tested specifically in perimenopausal and postmenopausal women with MDD in large, placebo-controlled RCTs (Clayton *et al.* 2013; Kornstein *et al.* 2010). In these RCTs, desvenlafaxine showed efficacy in both the perimenopausal and postmenopausal groups when dosed at 100-200 mg/day (Kornstein *et al.* 2010) and 50 mg/day (Clayton *et al.* 2013). At the recommended lower dosage of 50 mg/day, desvenlafaxine reduced depressive symptoms, alleviated pain intensity, and improved functioning (Clayton *et al.* 2013). Both studies showed that desvenlafaxine was well tolerated.

Although no other antidepressants have been investigated in large, placebo-controlled RCTs in a sample of well-defined perimenopausal or postmenopausal women with MDD, small, open-label studies support the efficacy of the SSRIs citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine as well as the SNRIs venlafaxine, desvenlafaxine, and duloxetine in treating depression in this population (Maki *et al.* 2018, 2019).

Based on a pooled analysis of eight RCTs, women ages 50 and up had a 28% chance of remitting on an SSRI but a 48% chance on the SNRI venlafaxine (Thase *et al.* 2005), suggesting that venlafaxine may be more effective for perimenopausal and postmenopausal women (although menopausal status was not formally evaluated in the pooled analysis). This is in contrast to a large, double-blind RCT that did not find a significant difference in efficacy between the SNRI desvenlafaxine and the SSRI escitalopram in treating MDD in postmenopausal women (Soares *et al.* 2010) and a post hoc analysis of clinical trial data that did not find a difference in efficacy between SNRI venlafaxine and SSRIs in older women (Kornstein *et al.* 2014). In postmenopausal women, the remission rate in those taking venlafaxine versus fluoxetine was 52% versus 55% at the acute phase endpoint and 71% versus 63% at the continuation phase endpoint (Kornstein *et al.* 2014).

For perimenopausal women, bupropion (a norepinephrine-dopamine reuptake inhibitor) or vortioxetine (a serotonin modulator and stimulator) is sometimes prescribed because these medications are less likely than SSRIs and SNRIs to cause sexual dysfunction, weight gain, or sleepiness (Jacobsen *et al.* 2015; Schatzberg *et al.* 2014; Serretti and Chiesa 2009). To date, however, no double-blinded RCTs of bupropion or vortioxetine have been conducted in a well-defined sample of perimenopausal or postmenopausal women.

Of patients in the general population who try at least two successive trials of antidepressants at an adequate dosage and duration, a third of patients do remit (Rush *et al.* 2006). In selecting treatment for women experiencing a major depressive episode in the menopause transition, the prescriber should consider whether a patient has had an adequate response to a particular antidepressant in the past (as that should guide treatment selection), available data on efficacy and tolerability in perimenopausal and postmenopausal women, burdensome adverse effects (e.g., sexual dysfunction, weight changes), and safety (e.g., drug-drug interactions) (Maki *et al.* 2019). Although the side effects of SSRIs and SNRIs may exacerbate some menopause-related symptoms, many of these antidepressants improve other menopause-related complaints, such as VMS, sleep problems, and pain (Guthrie *et al.* 2018; Joffe *et al.* 2013, 2014; Maki *et al.* 2019). Paroxetine is the only antidepressant with FDA approval for treatment of VMS (Orleans *et al.* 2014); however, escitalopram, citalopram, venlafaxine, desvenlafaxine, and vortioxetine also have evidence to support effectiveness in this context (Freeman *et al.* 2017; Handley and Williams 2015; Santoro *et al.* 2015). Fluoxetine and sertraline may be less effective for VMS and so are considered second-line treatment options (Handley and Williams 2015). Practically, the efficacy of antidepressants in the treatment of VMS typically occurs at the lower end of the dosage range for treating depression, so titrating to a dosage that adequately treats depressive symptoms is likely to treat VMS as well.

Hormone Therapy

Although estrogen is ineffective in treating depression in postmenopausal women, it may be effective during perimenopause (Maki *et al.* 2018). In fact, four small studies, including two RCTs, have demonstrated that estradiol is effective in alleviating depressive disorders during perimenopause (Cohen *et al.* 2003; Rasgon *et al.* 2001; Schmidt *et al.* 2000; Soares *et al.* 2001). In addition, the effects on depression lasted even after a 4-week washout period, when VMS and night sweats had reemerged (Soares *et al.* 2001), suggesting that although VMS and sleep problems may affect risk for psychological distress (Joffe *et al.* 2009), they are not the underlying cause of the depression.

One RCT tested whether hormone therapy ((estradiol 0.1 mg/day via transdermal patch plus intermittent oral micronized progesterone 200 mg/day for 12 days every 3 months) given to euthymic perimenopausal or early postmenopausal women was effective at reducing the risk of developing depression (Gordon *et al.* 2018). It was particularly effective at preventing depression for women in early perimenopause. However, current evidence is not sufficient to recommend use of estrogen-based therapies for asymptomatic perimenopausal and postmenopausal women to prevent depression because the risks may not outweigh the benefits (Maki *et al.* 2019).

While it is common for perimenopausal women to be prescribed COCs to prevent unintended pregnancies, manage VMS, and preserve bone mineral density (Miller *et al.* 2018), there are no RCTs focusing on the use of combined estrogen plus progesterone for the treatment of depression in perimenopausal women (Maki *et al.* 2018). For women with depressive disorders, including MDD, COCs should be considered, particularly for early perimenopausal women with VMS because risk for unintended pregnancy is not inconsequential (Santoro 2016). However, antidepressant therapy should also be considered because there is no evidence that COCs will treat MDD in perimenopausal women.

Despite the profound impact of estradiol on serotonergic function (Bethea *et al.* 2002; Lasiuk and Hegadoren 2007; Shanmugan and Epperson 2014), study findings are mixed regarding whether estrogen administration augments or accelerates response to SSRIs in postmenopausal women with depression (reviewed in Maki *et al.* 2018). However, in a pooled analysis of eight RCTs, use of hormone therapy in postmenopausal women eliminated the difference in response rate to SSRIs otherwise observed between premenopausal and postmenopausal women (Thase *et al.* 2005). A small RCT found that conjugated equine estrogen augmented the effects of antidepressant medication in perimenopausal women with MDD (Morgan *et al.* 2005). Despite these promising findings, such therapies should be used with caution and preferably when other menopausal symptoms are also present, such as VMS.

Clinical practice guidelines from NAMS recommend restricting hormone therapy to the treatment of symptoms related to the hypogonadal state of menopause (Pinkerton *et al.* 2017). At present, hormone therapy has FDA approval for four indications: bothersome VMS, genitourinary symptoms, prevention of bone loss, and premature hypoestrogenism (Pinkerton *et al.* 2017). The recommendation for treatment is to administer the lowest effective dosage for the shortest duration possible. Currently, estrogen therapy is not FDA approved for the treatment of perimenopausal depression. Nevertheless, growing evidence in placebo-controlled trials indicates that it can be effective in alleviating depressive symptoms when prescribed for women who have experienced perimenopausal (but not postmenopausal) onset of depression. Numerous peer-reviewed publications support the hypothesis that a window of opportunity exists for the effective use of estrogen therapy in managing depressive symptoms during the menopause transition (Maki *et al.* 2019).

Summary: Treatment of Major Depressive Disorder in Perimenopause

Based on the evidence reviewed herein, women with a history of MDD during premenopause who experience a relapse in depression during perimenopause should be treated first with the psychopharmacology regimen that worked best in the past. If they have significant menopausal symptoms, such as hot flashes or night sweats, particularly if these lead to sleep disturbance, a provider may choose to add a COC or another hormonal intervention. Concerns about unintended pregnancy may lead the provider to choose a COC over transdermal estradiol. For those with an intact uterus, the use of a progestogen is critical. COCs certainly protect the uterine endometrium from hyperplasia; however, other forms and ways of taking progestins may have fewer adverse mood effects, particularly if the route of administration is an IUD or vaginally administered cream that passes hepatic metabolism.

For women with new onset of MDD during perimenopause, the evidence is sufficient to support consideration of estradiol as a primary treatment. If MDD resolves after 4-6 weeks of estradiol alone, progesterone should be administered to reduce the risk of endometrial hyperplasia. Close monitoring of mood is necessary because progesterone administration can worsen mood (Toffol *et al.* 2015). Regardless of reproductive stage and menopausal symptoms, however, the provider should take the severity of MDD into consideration and use pharmacotherapy that is FDA approved for the treatment of MDD when necessary.

Schizophrenia

In contrast to schizophrenia in men, which has a peak onset at age 21-25 years, schizophrenia in women has a first peak in onset at 25-30 years and a second peak during midlife, around the time of the menopause transition (Gogos *et al.* 2015; Hafner 2003; McGrath *et al.* 2008). It is thought that estrogen protects against psychosis, which is why, when estrogen levels fall with the onset of the menopause, women show a second period of susceptibility to developing psychotic symptoms or schizophrenia (Gonzalez-Rodriguez and Seeman 2018) or a worsening of symptoms for women with preexisting schizophrenia (Sajatovic *et al.* 2000, 2003).

Antipsychotics

After menopause, psychotic symptoms increase, which may warrant the use of higher dosages of antipsychotics (Crawford and DeLisi 2016; Gonzalez-Rodriguez and Seeman 2018). However, the incidence of side effects increases after menopause, and not only because menopausal women often need higher dosages (Barbui *et al.* 2005; Brzezinski *et al.* 2017; Seeman 2012b). Because female sex and advancing age increase susceptibility to QTc interval prolongation, postmenopausal women taking antipsychotics that can prolong the QTc interval should be monitored carefully (Seeman 2012b). Furthermore, cardiovascular risk should be monitored closely in this population given that antipsychotics, age, and estrogen loss all heighten vulnerability (Carr 2003). Furthermore, most antipsychotics induce hyperprolactinemia (Meaney and O'Keane 2007), which exacerbates the menopause-induced decline in estrogen (Gonzalez-Rodriguez and Seeman 2018).

The unfavorable shift in androgen-to-estrogen ratio can lead to acne, hirsutism, sexual dysfunction, and osteoporosis (Gonzalez-Rodriguez and Seeman 2018; Meaney and O'Keane 2007). It is recommended that physicians avoid prescribing antipsychotics that cause QTc interval prolongation, hyperprolactinemia, weight gain, and extrapyramidal symptoms (Gonzalez-Rodriguez and Seeman 2018); however, this leaves only partial dopamine agonist antipsychotics, which are problematic for many individuals with schizophrenia (Takase *et al.* 2015). To balance side effects and treatment efficacy, physicians should keep antipsychotic dosages as low as possible, avoid polypharmacy unless necessary, and try intramuscular depot injections if oral antipsychotics are ineffective (Seeman 2012b).

Hormone Therapy

Because of fluctuating gonadal hormones, augmenting antipsychotic medication with estrogen therapy may be helpful in perimenopause (Kulkarni *et al.* 2019). Based on evidence-based clinical practice guidelines, the first-line estrogen treatment is transdermal estradiol (50 or 100 mcg), plus progestin if the woman has a uterus (Kulkarni *et al.* 2019). Progestin should be micronized, such as natural progesterone products like Prometrium (100 mg oral or vaginal). However, if estrogen therapy is contraindicated (due to breast or uterine pathology), then raloxifene (120 mg/day oral) could be tried. Because of the risk of thromboembolism, women who smoke more than 20 cigarettes/day, are very sedentary, or are overweight should receive estrogen therapy with caution. Unfortunately, the high rates of smoking, obesity, and cardiovascular disease in women with schizophrenia (Hennekens *et al.* 2005) mean the use of hormone therapy is limited in this population.

It is not recommended that women start estrogen therapy after the age of 60 years, but it is acceptable to continue hormone therapy beyond this age if it was started in perimenopause and if appropriate safety monitoring is done (Sturdee *et al.* 2011). In women without a hysterectomy, estrogens must be combined with progesterone to prevent endometrial carcinoma.

Concerns about the adverse impacts of estrogen plus progestin treatment have led to the development of selective estrogen receptor modulators (SERMs), which may be a safer alternative to standard hormone therapy because these drugs can act as an estrogen agonist and antagonist depending on the target tissue (An 2016). Estrogen modulators as adjunctive treatment options hold therapeutic promise (Gonzalez-Rodriguez and Seeman 2018). Raloxifene, a second-generation SERM, is the only SERM currently FDA approved for long-term treatment and is approved for the treatment of osteoporosis (An 2016).

Adjunctive use of raloxifene, at least for some women, helps keep antipsychotic dosages low (Gonzalez-Rodriguez and Seeman 2018). Three recent meta-analyses of RCTs support the use of raloxifene as a safe and effective treatment option for postmenopausal women with schizophrenia (de Boer *et al.* 2018; Wang *et al.* 2018; X. M. Zhu *et al.* 2018). Raloxifene is effective in alleviating overall schizophrenia symptom severity and positive and negative symptoms; however, it is not effective in improving cognitive functioning and alleviating comorbid depression (de Boer *et al.* 2018). Raloxifene may be more efficacious for patients with less severe schizophrenia; however, more research is needed (Wang *et al.* 2018). Although raloxifene increases the risk for venous thromboembolic events (Ellis *et al.* 2015), the absolute risk is low, as exemplified by an increase of 1.2 women per 1,000 women annually in a study in which women with cardiovascular disease or multiple risk factors were given 60 mg/day of raloxifene (Barrett-Connor *et al.* 2006).

Summary: Treatment of Schizophrenia in Perimenopause

The higher dosages of antipsychotics often needed for menopausal women and the increase in susceptibility to adverse effects in older age can lead to a substantial side-effect burden in menopausal women with schizophrenia and have implications for

antipsychotic choice, dosing strategy, and hormone therapy consideration. Regardless of whether adjunctive hormone therapy is used alongside antipsychotics, menopausal women should be examined for side effects, screened regularly for cancer and osteoporosis, and monitored routinely for metabolic and cardiovascular markers (Gonzalez-Rodriguez and Seeman 2018). For older women taking estrogen-based therapy, the following physical health screening procedures are recommended: assessment of breast health (e.g., ultrasound + mammogram every 2 years after age 50 years, physical examination, family history, BRCA gene testing if indicated), full cardiac function (especially if the patient is taking clozapine), clotting profile on full blood examination, cholesterol levels, cancer markers (CA125), cervix smear test (in sexually active women), and thyroid, liver, and renal function tests (Kulkarni *et al.* 2019).

Treating Cognitive Complaints During the Menopause Transition

Cognitive decline is a common complaint during perimenopause and early postmenopause (Maki and Henderson 2016). In one large longitudinal study, immediate and delayed recall declined from the premenopausal to the postmenopausal stage (Epperson *et al.* 2013). Furthermore, women who had undergone surgical menopause experienced a faster decline of verbal memory, semantic memory, and processing speed (Georgakis *et al.* 2019). Although one longitudinal study indicated that while cognitive problems are evident during the menopause transition, cognitive function may return to premenopausal levels after menopause (Greendale *et al.* 2009), in a meta-analysis of four cross-sectional studies, phonemic verbal fluency and delayed verbal memory worsened from perimenopause to postmenopause (Weber *et al.* 2014).

One double-blind, placebo-controlled crossover study found that after taking the psychostimulant lisdexamfetamine 40-60 mg/day for 4 weeks, menopausal women with new-onset executive functioning (EF) complaints showed significantly greater improvement in subjective and objective measures of EF relative to women who received placebo (Epperson *et al.* 2015; Shanmugan *et al.* 2017). The difference between baseline and posttreatment assessments in the lisdexamfetamine group indicated a large effect size on a measure of self-reported EF, with a medium effect size for superiority of lisdexamfetamine over placebo (Epperson *et al.* 2015). The effect sizes for improved performance on the delayed paragraph recall task were small to medium.

A double-blind, placebo-controlled crossover study tested the efficacy of atomoxetine 80 mg/day, a selective norepinephrine reuptake inhibitor, in improving EF difficulties in healthy women who reported midlife onset of difficulties with memory, concentration, and attention (Epperson *et al.* 2011). Atomoxetine was superior to placebo in reducing subjective working memory complaints but did not differ from placebo on neuropsychological tests and behavioral assessments. The improvement from baseline in women taking atomoxetine indicated a medium to large effect size, although the effect size was small for the difference between atomoxetine and placebo.

Before trying psychostimulants, providers may consider prescribing vortioxetine, which has shown efficacy in treating cognitive problems in perimenopausal and early postmenopausal women in a small observational study (Freeman *et al.* 2017). Otherwise, providers may consider use of lisdexamfetamine for women with new-onset EF

difficulties in the menopause transition. Contraindications for psychostimulants should be considered in the overall evaluation, including symptomatic cardiovascular disease, hyperthyroidism, hypertension, active substance use disorder, or an active psychotic disorder (Greenhill *et al.* 2002). Because psychostimulants can increase blood pressure and heart rate, providers should monitor vital signs both at baseline and quarterly thereafter.

Avoiding Drug Interactions During Surgical and Chemical Menopause

Most antidepressants inhibit the metabolism of tamoxifen to its more active metabolites by the cytochrome P450 (CYP) 2D6 (CYP2D6) enzyme, reducing its anticancer effects (Desmarais and Looper 2009). A review provided clinical guidance on which antidepressants are safest to use with tamoxifen (Desmarais and Looper 2009). Paroxetine and fluoxetine have a strong effect on the metabolism of tamoxifen and should not be used. Bupropion may also affect tamoxifen metabolism, and therefore its use is not advised for women taking tamoxifen. Venlafaxine has little or no effect on tamoxifen metabolism and is considered the safest choice among the antidepressants. Desvenlafaxine is not metabolized by the CYP system and may be another safe option. Mirtazapine has not been studied extensively but seems to have minimal effect on CYP2D6. All other antidepressants inhibit CYP2D6 to some extent, with an effect size ranging from mild (e.g., citalopram, escitalopram) to moderate (e.g., sertraline, fluvoxamine, duloxetine).

Conclusion

This chapter reviewed the evidence that treating psychiatric problems in women requires consideration of hormonal changes and reproductive stage across the life span, not only during pregnancy and postpartum. Endogenous hormones can affect the effectiveness and tolerability of psychotropic medications, and, in turn, psychotropic medications can affect endogenous hormones. Therefore, when treating women, providers need to consider how the menstrual cycle affects psychiatric symptoms and how the menopause transition affects psychiatric as well as cognitive concerns and choose an appropriate treatment strategy with these reproductive events in mind.

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CHAPTER 63

Psychopharmacology During Pregnancy and Lactation

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Managing perinatal mental illness encompasses two concomitant health concerns (pregnancy and a psychiatric disorder) and must address the welfare of at least two patients (mother and child). Many nonpharmacological treatments are available for perinatal mental illness but are beyond the scope of the current chapter. Treatment options must be available, accessible, affordable, and effective for the illness, and in many cases this may involve pharmacotherapy. While definitive psychopharmacological treatment guidelines for perinatal illness remain elusive, there is a consensus that the principal clinical objective is to minimize infant exposure to the purported risks of both maternal mental illness and psychotropic medication. Reviews of the reproductive safety of psychotropic medications often provide cursory information about the impact of illness, rely on maternal report to address concomitant fetal exposures, and use extensive statistical interrogation that may not have meaningful clinical import. This chapter reviews the extant data regarding psychotropic reproductive safety and addresses how those data may be applied in clinical decision-making.

Maternal-Fetal Risk Assessment

Minimizing Infant Exposure

Management of any perinatal medical condition must address the reproductive safety of available therapies, the likelihood of illness recurrence without continued treatment, and the potential impact of untreated maternal illness. Minor ailments are routinely treated during pregnancy. Consequently, 90% of pregnant women take at least one medication, and over 50% take four or more medications (Ayad and Costantine 2015; Mitchell *et al.* 2011). Conversely, women with mental illness are often encouraged to discontinue psychotropic medication during pregnancy and lactation. Pregnancy is associated with high rates of antidepressant discontinuation (Petersen *et al.* 2011) and psychotropic nonadherence (Lupattelli *et al.* 2015).

Risks of Perinatal Mental Illness

Although the desire to avoid exposing the child to psychotropic medication is laudable, these decisions are often made with little awareness of risks attributable to maternal mental illness. Both the likelihood of perinatal recurrence or exacerbation and the evidence that the illness may be harmful to the child warrant attention.

A patient's likelihood of perinatal recurrence may be estimated by synthesizing prevalence data from epidemiological studies with evidence from the patient's own history. Patients with frequent episodes of psychiatric illness, a declining course, or a previous history of perinatal illness are more likely to become ill in the current puerperium. Studies of the course of maternal mental illness have found no evidence that pregnancy offers protection from relapse, and there is considerable evidence that the postpartum period entails heightened vulnerability. The incidence of depression during the perinatal period has been found to be comparable to the incidence of depression during nonperinatal periods (Buesching *et al.* 1986; Cutrona 1983; Kumar and Robson 1984; Manly *et al.* 1982; O'Hara *et al.* 1982; Watson *et al.* 1984). Two large studies, collectively comprising 122,400 women, found a 14%-20% incidence of prenatal major depressive disorder (MDD) (Marcus *et al.* 2003; Oberlander *et al.* 2006). In fact, 11% of women presenting for evaluation of postpartum depression reported symptom onset before delivery (Stowe *et al.* 2005). Discontinuation of treatment during pregnancy in women with histories of MDD or bipolar disorder increases the risk of episodes during pregnancy (L. S. Cohen *et al.* 2006; Newport *et al.* 2008c; Viguera *et al.* 2007b), although a recent meta-analysis indicated that among women with a history of MDD, only those with indicators of more severe depression (i.e., earlier age at onset, greater number of prior episodes, depression treated in a psychiatric rather than an obstetrical clinic) were at heightened risk for prenatal recurrence after antidepressant discontinuation (Bayrampour *et al.* 2020). Psychotic disorders may also worsen during pregnancy (Glaze *et al.* 1991; McNeil *et al.* 1984a, 1984b). The course of OCD appears to be variable during pregnancy, with 14%-33% of patients experiencing exacerbation (Guglielmi *et al.* 2014; Jenike *et al.* 1990; Williams and Koran 1997). Women with OCD who remained on pharmacotherapy throughout the perinatal period did not demonstrate a significant change in symptoms (House *et al.* 2016). Panic disorder during gestation has also been found to be variable, with 19% of patients experiencing

more frequent panic attacks and 30% experiencing less frequent attacks (Hertzberg and Wahlbeck 1999; Wisner *et al.* 1996a). Finally, obstetrical trauma and pregnancy loss can precipitate PTSD (Allen 1998; Engelhard *et al.* 2001; Fones 1996), with PTSD symptoms following stillbirth persisting into the next pregnancy (Turton *et al.* 2001).

Postpartum mental illness has been documented for millennia and is substantiated by modern research. Psychiatric hospitalization rates spike in the first postpartum month (Kendler *et al.* 1993), and up to 12.5% of all psychiatric admissions for women occur in the first postpartum year (Duffy 1983). Postpartum depression affects 10%-22% of adult mothers and up to 26% of adolescent mothers (Stowe and Nemeroff 1995; Troutman and Cutrona 1990). Women with bipolar disorder also face considerable postpartum risk (Kendell *et al.* 1987; Targum *et al.* 1979). Postpartum OCD may affect 9%-16% of new mothers (Miller *et al.* 2013; Zambaldi *et al.* 2009), with one-third of those experiencing de novo onset of OCD (Miller *et al.* 2013). Postpartum psychosis, the most severe postpartum syndrome, is thankfully rare, but its prevalence is 100 times higher among women with bipolar disorder (Brockington *et al.* 1982; Kendell *et al.* 1987).

The dangers posed by perinatal mental illness, for both mother and child, must also be considered. Maternal depression during pregnancy has been associated with slower fetal growth (Hedegaard *et al.* 1996; Schell 1981; Uguz *et al.* 2013), increased risk of preterm delivery and other obstetrical complications (Korebrits *et al.* 1998; Liu *et al.* 2016; Oberlander *et al.* 2006; Orr and Miller 1995; Perkin *et al.* 1993; Steer *et al.* 1992; Uguz *et al.* 2013; Venkatesh *et al.* 2016), and persistent cognitive, behavioral, and emotional problems in the child (Luoma *et al.* 2001, 2004; Meijer 1985; Nulman *et al.* 2002; O'Connor *et al.* 2003; Sondergaard *et al.* 2003; Stott 1973). Similarly, prenatal panic disorder is associated with preterm birth, low birthweight (Uguz *et al.* 2013), and gestational hypertension (Newport *et al.* 2016), and maternal anxiety is associated with higher rates of attentional problems in the child (Van den Bergh and Marcoen 2004). Depressed pregnant women are less compliant with prenatal vitamins and obstetrical care, receive poorer nutrition, and have greater use of prescription opioids, hypnotics, alcohol, tobacco, and illicit substances (Newport *et al.* 2012; Zuckerman *et al.* 1989). Finally, depressed pregnant women, and those with PTSD, often experience suicidal thoughts (Newport *et al.* 2007b; Smith *et al.* 2006) and may engage in suicidal behavior.

Postpartum depression also carries deleterious developmental consequences. As early as 3 months, infants of mothers with depression exhibit less facial expression, less head orientation, less crying, and more fussiness than infants of nondepressed mothers (Martinez *et al.* 1996). The children of depressed mothers manifest ineffective emotion regulation (Downey and Coyne 1990), delayed motor development (Galler *et al.*

2000), poor interpersonal interactions (Jameson *et al.* 1997), lower self-esteem (Downey and Coyne 1990), increased fear and anxiety (Lyons-Ruth *et al.* 2000), more aggression (Jameson *et al.* 1997), and more insecure and disorganized attachment behaviors (Martins and Gaffan 2000). Children of depressed mothers are ultimately more likely to experience emotional instability, to have behavioral problems, to exhibit suicidal behavior, and to need psychiatric treatment (Lyons-Ruth *et al.* 2000; Weissman *et al.* 1984).

Perinatal exacerbation of schizophrenia and other psychotic illnesses also warrants concern. Women with schizophrenia have a higher prevalence of substance abuse

during pregnancy (Miller and Finnerty 1996; Taylor *et al.* 2015) and may exhibit bizarre ideas about contraception, pregnancy, and child rearing that complicate their perinatal course (McEvoy *et al.* 1983; Riordan *et al.* 1999). Maternal schizophrenia has been associated with elevated rates of obstetrical complications (Bennedsen *et al.* 2001; Miller and Finnerty 1996) and perinatal death (Rieder *et al.* 1975).

The clinical data regarding the obstetrical and developmental consequences of maternal mental illness are supported by an extensive line of laboratory animal research. Preclinical studies across a variety of species indicate that stress during pregnancy and the early postpartum period adversely affects offspring growth, learning ability, and postnatal development, producing a range of biobehavioral aberrations that may persist into adulthood (for a review, see Newport *et al.* 2002).

Risks of Perinatal Psychotropic Exposure

The risks of psychotropic exposure may be broadly classified as acute or developmental adverse effects (Table 63-1). Acute effects (e.g., drug toxicity and withdrawal) are typically evident immediately and are not dependent on the developmental window of exposure. Developmental effects, by definition, are dependent on the developmental window of exposure and are often not evident until later. These include somatic teratogenesis (i.e., major and minor malformations) and neurobehavioral teratogenesis (i.e., alterations in brain development that affect the child's subsequent behavior, cognitive abilities, and emotional regulation). The window of vulnerability to somatic teratogenesis is limited to the embryonic phase of development; however, the fetus and breastfeeding infant are theoretically vulnerable to neurobehavioral teratogenesis.

TABLE 63-1. Potential risks of perinatal medication exposure

	Acute	**Developmental**
Pregnancy	Neonatal toxicity Neonatal withdrawal Drug-drug interactions	Somatic teratogenesis Neurobehavioral teratogenesis
Lactation	Infant toxicity Drug-drug interactions	Neurobehavioral teratogenesis

Psychotropic treatment during pregnancy and lactation has complicated clinical, ethical, and potentially legal consequences. Although reproductive safety data address such concerns, methodological shortcomings in some studies undermine the reliability of these data. Most glaring are the frequent lack of appropriate control groups and an overreliance on retrospective data collection--deficiencies demonstrated to introduce biases that potentially lead to overestimation of the impact of psychotropic exposure (Newport *et al.* 2008a). In particular, many studies rely on control groups of healthy volunteers, eliminating any opportunity to disentangle treatment from illness effects (McDonagh *et al.* 2014). Despite these limitations, ethical considerations preclude implementation of randomized clinical trials to evaluate the reproductive safety of psychotropics. The reproductive safety database for psychotropics thus consists of a diverse conglomeration of observational studies, case reports, case series by pharmaceutical companies and academic centers, birth registries, retrospective surveys, reports from teratology or poison control centers, clinical and preclinical pharmacokinetic investigations, review articles summarizing data from these sources, and medication safety rating systems.

FDA Pregnancy and Lactation Labeling Rule

The FDA's new Pregnancy and Lactation Labeling Rule (PLLR) was launched in 2015 with a plan for staggered implementation over the following 3-5 years. The PLLR replaced the long-standing pregnancy letter category with the following information: pregnancy exposure registration, narrative risk summary, clinical considerations, and data description of supporting evidence. In addition to pregnancy and lactation profiles, the PLLR also summarizes evidence for "males and females of reproductive potential." The PLLR is subject to ongoing updates as evidence emerges but is required only for medications receiving FDA approval after June 30, 2001.

Antidepressants

The use of antidepressant medications in pregnancy has been extensively reviewed (McDonagh *et al.* 2014; Yonkers *et al.* 2014), and multiple meta-analyses have found no association between antidepressant use in pregnancy by women with psychiatric illness and the risk for major malformations (T. R. Einarson and Einarson 2005; Gao *et al.* 2018; Grigoriadis *et al.* 2013). Overviews of the individual categories of antidepressants are included below.

Selective Serotonin Reuptake Inhibitors

Reproductive safety data on the selective serotonin reuptake inhibitors (SSRIs) have rapidly accrued in recent decades. Meta-analyses investigating SSRIs found no overall association with birth defects among infants of women with psychiatric illness (Gao *et al.* 2018; Reefhuis *et al.* 2015). Despite overall reassuring data, some concerns with specific SSRIs have emerged. Reefhuis *et al.* (2015) found an increased risk of anencephaly, atrial septal defects, right ventricular outflow tract obstruction, gastroschisis, and omphalocele with paroxetine exposure and an increased risk of right ventricular outflow track obstruction defects and craniosynostosis with fluoxetine. A meta-analysis of fluoxetine outcomes also reported an association (OR = 1.36) with cardiovascular malformations (Gao *et al.* 2017). Analysis of a managed care database revealed a higher odds ratio for cardiovascular malformations with exposure to paroxetine compared with other antidepressants (GlaxoSmithKline 2005). Three large case-control studies (Alwan *et al.* 2007; Berard *et al.* 2007; Louik *et al.* 2007) have produced largely reassuring results, though with some concerns. The first (Alwan *et al.* 2007) reported small increases in the risk for three uncommon malformations: anencephaly (OR = 2.4), craniosynostosis (OR = 2.5), and omphalocele (OR = 2.8). The second study (Louik *et al.* 2007) reported an increased risk for omphalocele (OR = 5.7) and septal defects (OR = 2.0) with sertraline exposure and for right ventricular outflow tract obstruction defects (OR = 3.3) with paroxetine exposure. The third study (Berard *et al.* 2007) found no evidence of increased risk for cardiovascular or other malformations with SSRI use, unless women were taking more than 25 mg of paroxetine per day, in which case an increased risk for cardiovascular (OR = 3.1) and overall malformations (OR = 2.2) was observed. Using the Medicaid Analytic eXtract database, Huybrechts *et al.* (2014a) found an overall adjusted risk of 1.06 (95% CI, 0.93-1.22) for any cardiac defect with the use of SSRIs in the first trimester, a risk of 1.07 (95% CI, 0.59-1.93) for right ventricular outflow tract obstruction with the use of paroxetine, and a risk of 1.04 (95% CI, 0.76-4.41) for ventricular septal defects with the use of sertraline.

A handful of studies have systematically assessed child development after prenatal exposure to antidepressants. Two studies (Nulman *et al.* 1997, 2002) assessed children (ages 15-86 months) who had been prenatally exposed to fluoxetine (*n* = 90) or tricyclic antidepressants (TCAs) (*n* = 126), collectively comparing them with nonexposed children (*n* = 120). No differences were observed with respect to global cognitive, psychomotor, or language development. The same group compared children who had been exposed to SSRIs in utero with children born to mothers without depression and found no differences in IQ or behavior (Nulman *et al.* 2012). A similar study that compared children (ages 6-40 months) with prenatal SSRI exposure (*n* = 31) and children without antidepressant exposure (*n* = 13) observed no differences in global cognition but reported lower psychomotor scores for the SSRI-exposed children (Casper *et al.* 2003). Unfortunately, limitations of these studies render their implications speculative at best. Children were not age-matched in any of these studies, and the predictive validity of these indices across child developmental stages has not been established (Black and Matula 2000). In addition, the Casper *et al.* (2003) study was confounded by the fact that 29% of the participants were enrolled after delivery, which could result in an overrepresentation of children with developmental abnormalities. A study of 69 (46 SSRI exposed, 23 nonexposed) children that eliminated the age confound by examining the children at two fixed time points--2 months and 8 months of age--reported no differences between the exposed and nonexposed children in cognitive or motor development (Oberlander *et al.* 2004). Finally, an assessment of 4-year-old children found no evidence that prenatal SSRI exposure affected externalizing or attentional behaviors (Oberlander *et al.* 2007). It is noteworthy that several of these developmental studies involved a significant overlap between cohorts of children, thereby limiting further the cumulative sample size of extant follow-up studies.

A rapidly emerging literature including 14 studies within 10 years has explored whether there is an association between prenatal antidepressant use and autism spectrum disorders in offspring. At first glance, the results appear to be decidedly mixed; however, closer inspection reveals evidence of an ascertainment bias due to ethnic disparities in access to health care among studies using a population-based control group (Vega *et al.* 2020). Studies overcoming this source of bias by using a discordant sibling comparison group demonstrated no connection between fetal antidepressant exposure and subsequent diagnosis of autism (OR = 0.85).

Data regarding the impact of prenatal antidepressant exposure on rates of miscarriage, preterm delivery, and low birthweight are decidedly mixed. Some investigators have reported an association with such outcomes (Chambers *et al.* 1996; Chang *et al.* 2020; Chun-Fai-Chan *et al.* 2005; Eke *et al.* 2016; Oberlander *et al.* 2006; Pastuszak *et al.* 1993; Ross *et al.* 2013; Simon *et al.* 2002; Vlenterie *et al.* 2021), whereas others have not found this association (Einarson *et al.* 2001, 2003; Kulin *et al.* 1998; Sivojelezova *et al.* 2005; Venkatesh *et al.* 2016). Multiple meta-analyses have found an association between prenatal antidepressant exposure and preterm delivery (Chang *et al.* 2020; Eke *et al.* 2016; Huang *et al.* 2014; Huybrechts *et al.* 2014b; Ross *et al.* 2013; Vlenterie *et al.* 2021) and low birthweight (Huang *et al.* 2014; Ross *et al.* 2013). However, interpretation is complicated by other reports that prematurity and low birthweight are associated with prenatal maternal depression and anxiety (Fekadu Dadi *et al.* 2020; Ghimire *et al.* 2021; Grigoriadis *et al.* 2018; Jarde *et al.* 2016), and there is a lack of precision in efforts to control for the confounding effect of maternal mental illness in studies to date. As a result, no definitive conclusions can be drawn as to whether antidepressant use during gestation conveys an adverse impact on fetal growth or the timing of parturition.

Finally, concerns have been expressed about neonatal SSRI syndromes, manifested by a variable constellation of transient respiratory, cardiovascular, gastrointestinal, motor, and central nervous system symptoms (Moses-Kolko *et al.* 2005). A recent meta-analysis (Kautzky *et al.* 2022), identifying only 33 qualifying controlled studies among 3,025 published reports, confirmed a statistically significant association between serotonin reuptake inhibitor exposure and symptoms of so-called poor neonatal adaptation syndrome; however, the authors bemoaned the fact that the "inherently low data quality in this research domain and insufficiently defined samples and outcomes" (p. 6) left them unable to draw conclusions about the clinical relevance of these data. Indeed, close scrutiny of this literature reveals many methodological shortcomings, including failure to adequately control for confounding and susceptibility to rater bias and ascertainment bias.

Debate has also focused on a more serious neonatal concern: a putative connection between late-pregnancy SSRI exposure and persistent pulmonary hypertension of the neonate (PPHN). A case-control study (Chambers *et al.* 2006) of 1,213 neonates (377 with PPHN) reported findings supporting an association between SSRI exposure and PPHN (OR

= 6.1). This lone report led the FDA in July 2006 to issue a Public Health Advisory regarding this reported link to PPHN (U.S. Food and Drug Administration 2006). Five years later, after a series of both positive and negative studies, the FDA issued an update advising that "conflicting studies [are] . . .making it unclear whether use of SSRIs during pregnancy can cause PPHN" (U.S. Food and Drug Administration 2011). Two meta-analyses (Masarwa *et al.* 2019; Ng *et al.* 2019) of the 11 studies to date reported a significant association (ORs = 1.52 and 1.82) between SSRI exposure and PPHN; Ng *et al.* (2019) estimated the risk difference attributable to antidepressant exposure at 0.619 per 1,000 live deliveries.

Pharmacokinetic data regarding the placental passage of SSRI antidepressants remain limited. However, existing studies have demonstrated that mean fetal/maternal ratios for numerous SSRIs and their active metabolites are uniformly less than 1.0, although considerable differences exist between agents (Heinonen *et al.* 2021; Hendrick *et al.* 2003; Rampono *et al.* 2009).

Published reports pertaining to SSRIs and lactation now encompass the largest dataset for medications during breastfeeding, including infant serum measures, breast milk concentrations, and pharmacokinetic studies of excretion. There are now published investigations for all of the SSRIs including sertraline (Altshuler *et al.* 1995; Birnbaum *et al.* 1999; Dodd *et al.* 2000; Epperson *et al.* 1997, 2001; Hendrick *et al.* 2001a; Kristensen *et al.* 1998; Mammen *et al.* 1997; Schoretsanitis *et al.* 2019; Stowe *et al.* 1997, 2003; Wisner *et al.* 1998), fluoxetine (Birnbaum *et al.* 1999; Burch and Wells 1992; Hendrick *et al.* 2001b; Kristensen *et al.* 1999; Lester *et al.* 1993; Suri *et al.* 2002; Taddio *et al.* 1996; Yoshida *et al.* 1998a), paroxetine (Birnbaum *et al.* 1999; Hendrick *et al.* 2001a; Ohman *et al.* 1999; Spigset *et al.* 1996; Stowe *et al.* 2000), escitalopram (Rampono *et al.* 2006; Weisskopf *et al.* 2020), fluvoxamine (Hendrick *et al.* 2001a; Piontek *et al.* 2001; Wright *et al.* 1991), and citalopram (Jensen *et al.* 1997; Schmidt *et al.* 2000; Schoretsanitis *et al.* 2019; Spigset *et al.* 1997; Weisskopf *et al.* 2020). Although infant follow-up data are limited, only a few isolated cases of adverse effects have been reported. Long-term neurobehavioral studies of infants exposed to SSRI antidepressants during lactation warrant continued examination. The pharmacokinetic profiles of breast milk excretion, including delineation of distribution gradients and time gradients, are best defined for sertraline (Stowe *et al.* 1997, 2003), paroxetine (Stowe *et al.* 2000), escitalopram (Weisskopf *et al.* 2020), and fluoxetine (Suri *et al.* 2002). These studies indicate that quantitative infant SSRI exposure during lactation is considerably lower than transplacental exposure.

Serotonin-Norepinephrine Reuptake Inhibitors

Although lagging considerably behind the SSRIs, reproductive safety data for serotonin-norepinephrine reuptake inhibitors (SNRIs) are steadily accruing. A multicenter case-control study including 71 prenatal venlafaxine exposures reported significantly higher rates of numerous malformations (ORs = 3.34-5.26) (Anderson *et al.* 2020). Previous studies collectively encompassing 862 venlafaxine exposures observed 91 (10.6%) major malformations among exposed infants (Einarson *et al.* 2001; GlaxoSmithKline 2005; Polen *et al.* 2013). As previously noted in the SSRI discussion, surveillance biases, particularly with respect to cardiovascular defects, cannot be ruled out. A Scandinavian cohort study including 1,512 duloxetine-exposed pregnancies found no evidence of increased risk for birth defects (OR = 0.98) (Ankarfeldt *et al.* 2021). An earlier study including 165 live births to women using duloxetine throughout pregnancy reported 3 (1.8%) major malformations (Einarson *et al.* 2012). To date, there are no reports regarding birth defect rates associated with exposure to desvenlafaxine or levomilnacipran.

There have been reports on neonatal and developmental outcomes following prenatal exposure to duloxetine and venlafaxine. A single report followed an infant until 9 months after in utero exposure to duloxetine, with no abnormalities in cognitive, language, motor, and psychomotor development (Bellantuono *et al.* 2013). Likewise, children exposed to venlafaxine in utero had no difference in IQ or behavior compared with children of nondepressed mothers (Nulman *et al.* 2012).

A nested case-control study reported that maternal exposure to SNRI antidepressants after the twentieth week of pregnancy was associated with an increased risk for hypertensive disorders of pregnancy (OR = 2.57; 95% CI, 1.34-4.93), with an even higher sixfold increase among mothers receiving venlafaxine at dosages exceeding 187.5 mg/day (Newport *et al.* 2016).

Prenatal pharmacokinetic data are limited. High rates of placental transfer (umbilical cord concentrations in excess of maternal concentrations) have been reported for venlafaxine (Hendrick *et al.* 2003) and for its active metabolite, desvenlafaxine (Hendrick *et al.* 2003; Rampono *et al.* 2009). Duloxetine has a single case report of a cord/maternal serum concentration ratio of 0.12, which suggests a low rate of placental transfer (Boyce *et al.* 2011).

Lactation data also remain limited. Best studied are venlafaxine/desvenlafaxine, for which three studies (Ilett *et al.* 1998; Newport *et al.* 2009; Rampono *et al.* 2011; Schoretsanitis *et al.* 2019) encompassing 26 mother-infant nursing dyads have reported relative infant doses (RIDs) of 6.8%-8.1%, which is within the notional 10% presumed safety level (Hendrick *et al.* 2003; Rampono *et al.* 2009). A single case report and a small series of 6 women receiving duloxetine therapy during lactation reported RIDs of less than 1% (Boyce *et al.* 2011; Lobo *et al.* 2008). There are no published lactation data for levomilnacipran.

Atypical Antidepressants

Reproductive safety data are more limited for the so-called atypical antidepressants (i.e., bupropion, mirtazapine, nefazodone, trazodone, vilazodone, and vortioxetine). Prospective reports of first-trimester use of these agents consist of 2,550 bupropion exposures producing 56 (2.2%) children with major malformations (Boshier *et al.* 2003; Briggs *et al.* 2005; Chun-Fai-Chan *et al.* 2005; Cole *et al.* 2007; GlaxoSmithKline 2005), 404 trazodone exposures with 10 (2.5%) major malformations (Briggs *et al.* 2005; GlaxoSmithKline 2005; McElhatton *et al.* 1996), 140 nefazodone exposures with 2 (1.4%) major malformations (GlaxoSmithKline 2005), 508 mirtazapine exposures with 14 (2.8%) major malformations (Djulus *et al.* 2006; GlaxoSmithKline 2005; Smit *et al.* 2015; Winterfeld *et al.* 2015), and a combined report of 121 nefazodone or trazodone exposures with 2 (1.7%) major malformations (Einarson *et al.* 2003). A lone case report of vilazodone use in pregnancy resulted in a full-term, healthy neonate (Morrison 2014). There are no published data on prenatal vortioxetine exposure. Neurodevelopmental data following prenatal exposure to atypical antidepressants are lacking, as are prenatal pharmacokinetic studies.

Lactation data also remain limited. The sole report of bupropion in nursing infants noted that the drug could not be detected in the plasma of a nursing infant (Briggs *et al.* 1993). Five reports totaling 55 neonates exposed to mirtazapine have been reported, with no adverse outcomes and low RIDs (Aichhorn *et al.* 2004; Klier *et al.* 2007; Kristensen *et al.* 2007; Smit *et al.* 2015; Tonn *et al.* 2009). There are no published lactation data for vilazodone or vortioxetine.

Mood Stabilizers

Lithium

Early retrospective data suggested that lithium exposure was associated with a 400-fold increase in cardiac malformations, specifically Ebstein's anomaly (Nora *et al.* 1974; Weinstein and Goldfield 1975). Subsequent large studies confirmed the concern for teratogenicity, but at a much lower magnitude (L. S. Cohen *et al.* 1994). Altshuler *et al.* (1996) estimated a 20-fold increase in the risk for Ebstein's anomaly, from 1:20,000 to 1:1,000 after prenatal lithium exposure. A U.S. cohort study (Patorno *et al.* 2017) observed a threefold risk increase for cardiac malformations when daily dosage exceeded 900 mg. Two recent meta-analyses (Fornaro *et al.* 2020; Munk-Olsen *et al.* 2018) reported that lithium exposure was associated with an even lower risk for overall major malformations (OR = 1.71-203); only one of these studies (Fornaro *et al.* 2020) found that lithium exposure was associated with cardiac defects (OR = 3.99). When lithium is used in pregnancy, a fetal echocardiogram between gestational weeks 18 and 20 is recommended. Deciding whether to continue lithium in pregnancy depends on the severity and course of the patient's illness and the time point of the exposure during gestation. Discontinuing lithium therapy once cardiogenesis nears completion at 9-11 weeks' gestation may be ill-advised.

Neurodevelopment sequelae of prenatal lithium exposure have not been demonstrated; however, evidence remains limited (Forsberg *et al.* 2018; Jacobson *et al.* 1992; Schou 1976; van der Lugt *et al.* 2012).

Two recent meta-analyses reported reassuring data on obstetrical complications following lithium exposure. In a comparison with illness-matched control subjects, lithium in pregnancy did not confer increased risk of miscarriage (Fornaro *et al.* 2020) or preeclampsia, gestational diabetes, fetal distress, postpartum hemorrhage, cesarean section, preterm birth, low birthweight, or small-for-gestational-age birth (Munk-Olsen *et al.* 2018). A large U.S. cohort study reported no increased risk of ischemic placental disease, preterm birth, or small-for-gestational-age birth (J. M. Cohen *et al.* 2019). Conversely, a recent retrospective cohort study found that prenatal lithium exposure (n = 119) was associated with increased fetal growth and birthweight (Poels *et al.* 2021).

Lithium's narrow therapeutic index raises concern for acute perinatal toxicity. In a pooled analysis of lithium placental passage and neonatal outcomes (Newport *et al.* 2005), we determined that 1) higher neonatal lithium concentrations were associated with significantly lower Apgar scores, longer hospital stays, and higher rates of CNS and neuromuscular complications; 2) umbilical cord (i.e., fetal) plasma concentrations were uniformly equivalent to maternal concentrations, confirming lithium's rapid transplacental equilibration; and 3) withholding lithium therapy for only 24-48 hours lowered lithium concentrations by 0.28 mEq/L. By contrast, a recent cohort study (Molenaar *et al.* 2021) observed no association between lithium levels and neonatal complications; however, the discrepancy with the earlier study may be attributable to the narrower range of observed lithium concentrations.

Alterations in renal clearance across pregnancy and the potential for abrupt volume changes during delivery mandate careful monitoring of lithium levels during pregnancy and at delivery. One study assessed longitudinally the peripartum pattern of maternal serum lithium, observing a decrease from the preconception level during the first and second trimesters and a gradual increase in the third trimester toward the preconception level (Wesseloo *et al.* 2017).

The existing database regarding lithium and lactation encompasses 43 mother-infant dyads (Bogen *et al.* 2012; Frew 2015; Fries 1970; Marin Gabriel *et al.* 2018; Moretti *et al.* 2003; Schou and Amdisen 1973; Skausig and Schou 1977; Sykes *et al.* 1976; Tanaka *et al.* 2008; Tunnessen and Hertz 1972; Viguera *et al.* 2007a; Weinstein and Goldfield 1969; Woody *et al.* 1971). Adverse events, including lethargy, hypotonia, hypothermia, cyanosis, electrocardiogram changes, poor feeding, slow growth, gross and fine motor delay, and elevated thyroid-stimulating hormone level, were reported in 6 (15%) of the 43 children collectively included in these case reports of lithium exposure via lactation. The American Academy of Pediatrics (Sachs and Committee on Drugs 2013) recommends monitoring growth and neurodevelopment in infants exposed to lithium during lactation. The hydration status of nursing infants of mothers taking lithium should also be carefully monitored (Llewellyn *et al.* 1998). Lithium

transfer to the infant from breast milk is variable, with lithium concentrations in nursing infants ranging from 5% to 67% of maternal levels (Newmark *et al.* 2019). The largest pharmacokinetic study calculated lithium's milk-to-plasma ratio as 53% and infant-to-maternal plasma ratio as 24% (Viguera *et al.* 2007a).

Lamotrigine

Reproductive safety data regarding lamotrigine have rapidly accrued and compare favorably with those of other mood stabilizers (Weston *et al.* 2016). Malformation rates after first-trimester lamotrigine exposure are consistent with those of the general population (Campbell *et al.* 2014; Cunnington *et al.* 2011; Dominguez-Salgado *et al.* 2004; GlaxoSmithKline 2007; Holmes *et al.* 2006; Meador *et al.* 2006; Molgaard-Nielsen and Hviid 2011; Morrow *et al.* 2006; Sabers *et al.* 2004; Vajda *et al.* 2003). A report by the North American Pregnancy Registry (Holmes *et al.* 2006) noted a high rate of orofacial clefts (0.89% of 564 exposures); the collective rate of orofacial clefts in the other registries was only 0.10% (3 per 2,956 exposures) (Dominguez-Salgado *et al.* 2004; GlaxoSmithKline 2007; Meador *et al.* 2006; Molgaard-Nielsen and Hviid 2011; Morrow *et al.* 2006; Sabers *et al.* 2004; Vajda *et al.* 2003). The UK Epilepsy and Pregnancy Register reported a higher risk of malformations at maternal dosages exceeding 200 mg/day (Morrow *et al.* 2006), although this finding was not confirmed in subsequent analyses (GlaxoSmithKline 2007; Molgaard-Nielsen and Hviid 2011; Patorno *et al.* 2017). Despite these reassuring findings, folate supplementation is recommended for all women of childbearing age who are taking any antiepileptic drug, including lamotrigine.

Prospective neurodevelopmental data have been consistently favorable for prenatal lamotrigine exposure (Baker *et al.* 2015; Coste *et al.* 2020; McVearry *et al.* 2009; Meador *et al.* 2006, 2009, 2011; Nadebaum *et al.* 2011b); however, a meta-analysis (Veroniki *et al.* 2017b) reported that lamotrigine exposure is associated with increased risk for autism (OR = 8.88; 95% CI, 1.28-112), although the wide confidence interval suggests caution in interpreting these results.

Lamotrigine clearance steadily increases across the gestational period (de Haan *et al.* 2004; Fotopoulou *et al.* 2009; Franco *et al.* 2008; Pennell *et al.* 2004, 2008; Petrenaite *et al.* 2005; Polepally *et al.* 2014; Reisinger *et al.* 2013; Tran *et al.* 2002), with changes evident as early as week 5 of gestation (Karanam *et al.* 2018); lamotrigine clearance abruptly declines after delivery (Ohman *et al.* 2000; Pennell *et al.* 2004; Polepally *et al.* 2014; Tran *et al.* 2002). Multiple dosage increases during pregnancy followed by a postpartum decrease may thus be necessary. Neonatal lamotrigine concentrations are equal to maternal concentrations (Myllynen *et al.* 2003; Ohman *et al.* 2000; Paulzen *et al.* 2015; Sathanandar *et al.* 2000; Tomson *et al.* 1997), indicating complete placental passage.

There have been no reports of acute adverse obstetrical or neonatal outcomes in association with prenatal lamotrigine exposure.

Reports regarding lamotrigine and lactation (Bedussi *et al.* 2018; Clark *et al.* 2013; GlaxoSmithKline 2007; Kacirova *et al.* 2019a; Liporace *et al.* 2004; Morin and Chevalier 2017; Newport *et al.* 2008c; Nordmo *et al.* 2009; Ohman *et al.* 2000; Page-Sharp *et al.* 2006; Rambeck *et al.* 1997; Tomson *et al.* 1997) encompass 145 mother-infant nursing dyads. The two largest lamotrigine lactation studies, collectively comprising 100 mother-infant pairs (Birnbaum *et al.* 2020; Newport *et al.* 2008b), reported mean infant-to-maternal

plasma ratios of 18.3%-28.9%. Adverse events were reported for 10 (6.9%) of these children, including apneic episodes (Nordmo *et al.* 2009), 7 infants with benign thrombocytosis (Newport *et al.* 2008b), anemia (Bedussi *et al.* 2018), weight loss, and dehydration (Morin and Chevalier 2017). In addition, the French Pharmacovigilance Database reported adverse reactions (sedation, hypotonia, weight loss, and liver damage) in 6 infants breastfed by mothers taking lamotrigine (Soussan *et al.* 2014). Long-term neurobehavioral outcomes have not been studied in nursing infants exposed to lamotrigine.

Valproate (Valproic Acid)

Prenatal exposure to valproate has been associated with multiple congenital malformations, including neural tube, cardiac, orofacial or craniofacial, and skeletal and limb defects, with an OR of 10.93 for overall major malformations (Weston *et al.* 2016). Two meta-analyses confirmed that valproate's teratogenicity exceeds that of other anticonvulsants (Veroniki *et al.* 2017a; Weston *et al.* 2016). Risks for spina bifida and for limb defects are estimated at 1%-2% (10-20 times greater than in the general population) (Bjerkedal *et al.* 1982; Centers for Disease Control and Prevention 1992; Rosa 1991) and 0.42% (i.e., 6.17 times higher than in the general population) (Rodriguez-Pinilla *et al.* 2000), respectively. Dosages higher than 1,500 mg/day have been linked with greatest risk (Weston *et al.* 2016). One group recommend not exceeding 1,000 mg/day and maintaining maternal serum concentrations below 70 mg/mL to reduce teratogenic risk (Kaneko *et al.* 1999). Valproate antagonism of folate activity may underlie the risk for both spina bifida and fetal valproate syndrome, a condition characterized by a distinctive pattern of facial dysmorphism and other malformations (McMahon and Braddock 2001; Moore *et al.* 2000). A case-control study of children with and without fetal anticonvulsant syndrome, who had all been exposed to an AED during gestation, found a significantly higher rate of homozygosity for a mutation in the methylenetetrahydrofolate reductase gene in the mothers of affected children (Dean *et al.* 1999).

Neurodevelopmental outcomes in offspring associated with prenatal valproate exposure are of equal concern (Baker *et al.* 2015; M. J. Cohen *et al.* 2013; Meador *et al.* 2009, 2013; Shallcross *et al.* 2011; Veiby *et al.* 2013), particularly in relation to verbal cognition (McVearry *et al.* 2009; Meador *et al.* 2011; Nadebaum *et al.* 2011a, 2011b). Prenatal valproate exposure has been associated with a 7-to 10-point reduction in IQ at 6 years of age (Meador *et al.* 2013), in line with findings at 3 (Meador *et al.* 2009), 3.6 (Coste *et al.* 2020), and 4.5 years (Meador *et al.* 2012). A recent Swedish population-based study (Wiggs *et al.* 2020) with 17 years of follow-up data estimated that prenatal valproate exposure confers a 2.3-fold higher risk for autism spectrum disorder and 1.7-fold higher risk for ADHD. The highest risk of neurodevelopmental disorders was found for dosages higher than 1,100 mg/day (Coste *et al.* 2020).

Valproate exposure during gestation is also associated with negative obstetrical outcomes, such as fetal loss (Veroniki *et al.* 2017a) and numerous fetal and neonatal toxicities, including hepatotoxicity (Kennedy and Koren 1998), coagulopathies (Mountain *et al.* 1970), and neonatal hypoglycemia (Ebbesen *et al.* 2000; Thisted and Ebbesen 1993). However, in a U.S. cohort study, prenatal valproate (n = 2,398) did not confer increased risk of ischemic placental disease, preterm birth, or small-for-gestational-age birth (J. M. Cohen *et al.* 2019).

Maternal valproate concentrations steadily decline across pregnancy (Yerby *et al.* 1990, 1992), especially during the final month (Nau *et al.* 1982b; Otani 1985; Philbert *et al.* 1985). Thus, dosage increases may be necessary to maintain therapeutic efficacy during pregnancy. Umbilical cord concentrations at delivery are greater than or equal to maternal concentrations (Froescher *et al.* 1984b; Philbert *et al.* 1985; Yerby *et al.* 1990, 1992).

The literature regarding valproate and lactation encompasses 72 mother-infant dyads (Alexander 1979; Bardy *et al.* 1982a; Dickinson *et al.* 1979; Froescher *et al.* 1981; Govindan and Mandadi 2021; Kacirova *et al.* 2019b;

Nau *et al.* 1981; Piontek *et al.* 2000; Stahl *et al.* 1997; Tsuru *et al.* 1988; von Unruh *et al.* 1984; Wisner and Perel 1998). Two adverse events were reported: thrombocytopenia and anemia (Stahl *et al.* 1997) and patchy hair loss (Govindan and Mandadi 2021). Valproate milk-to-plasma ratios are uniformly low, and serum concentrations of nursing infants are 2%-40% of maternal concentrations (Alexander 1979; Bardy *et al.* 1982a; Kacirova *et al.* 2019b; Piontek *et al.* 2000; Stahl *et al.* 1997; von Unruh *et al.* 1984; Wisner *et al.* 1996b). Breastfeeding exposure to valproate was not associated with cognitive delay in children at 3 (Meador *et al.* 2010) or 6 years of age (Meador *et al.* 2014).

Because of grave safety concerns, valproate should be used in women of childbearing age only as a last resort. If valproate must be used during pregnancy, its risk may be reduced by not exceeding a daily dosage of 1,000 mg and a serum concentration of 70 mg/mL. High-dose folate supplementation (4-5 mg/day) is recommended in valproate-treated women of reproductive age, although there is no conclusive evidence that such dosing reduces the risks associated with prenatal valproate exposure. Preliminary evidence that aspects of fetal valproate syndrome other than neural tube defects may be associated with valproate's antagonism of folate metabolism suggests that folate supplementation should be administered not only in the first trimester but throughout gestation. Because of the potential for valproate-associated neonatal coagulopathies, oral vitamin K supplementation (10-20 mg/day) may be considered during the final month of gestation. Prenatal surveillance for congenital abnormalities should include maternal serum alpha-fetoprotein, fetal echocardiography, and a level 2 ultrasound at approximately 16-18 weeks' gestation. Genetic screening of valproate-treated women for methylenetetrahydrofolate reductase mutations warrants future consideration. Although valproate therapy during lactation appears to be better tolerated, monitoring platelet count and serum liver enzymes of nursing infants is recommended.

Carbamazepine

Carbamazepine is associated with many of the same risks as valproate during gestation, although with less frequency or severity. For example, meta-analyses (Veroniki *et al.* 2017a; Weston *et al.* 2016) have found that the risk for major malformations (OR = 1.37-2.01) associated with carbamazepine exposure was markedly lower than that attributed to valproate (OR = 10.93) (Weston *et al.* 2016). Carbamazepine exposure confers a 0.5%-1.0% risk for neural tube defects (Rosa 1991), approximately half the magnitude of valproate (Lindhout and Schmidt 1986; Rosa 1991). Periconceptional folate supplementation has been associated with a lower rate of neural tube defects among children exposed to carbamazepine prenatally (Hernandez-Diaz *et al.* 2001). Heightened teratogenic risk has been reported at daily dosages exceeding 1,000 mg (Campbell *et al.* 2013; Tomson *et al.* 2011).

Systematic studies have generally failed to produce evidence of developmental delay in children exposed to carbamazepine prenatally (Baker *et al.* 2015; McVearry *et al.* 2009; Meador *et al.* 2006, 2009, 2011; Nadebaum *et al.* 2011b). However, data from the Swedish medical register (Wiggs *et al.* 2020) reported that first-trimester carbamazepine exposure (*n* = 1,417) was associated with a small elevated risk of autism spectrum disorder (hazard ratio = 1.26).

Obstetrical outcome data for carbamazepine have been favorable. Neonatal hepatotoxicity has been reported in one carbamazepine-exposed infant (Frey *et al.* 2002); however, a recent U.S. cohort study found no association between carbamazepine exposure (*n* = 1,232) and risk of ischemic placental disease, preterm birth, or small-for-gestational-age birth (J. M. Cohen *et al.* 2019).

Some investigators have reported significant increases in carbamazepine clearance during the third trimester of pregnancy (Battino *et al.* 1982; Dam *et al.* 1979; Lander *et al.* 1981), but others have found no changes (Bardy *et al.* 1982b; Johnson *et al.* 2014; Otani 1985; Reisinger *et al.* 2013; Yerby *et al.* 1985). Umbilical-cord-to-maternal plasma ratios are 0.5-0.8, a lower placental transfer than for other anticonvulsants (Nau *et al.* 1982a; Yerby *et al.* 1990, 1992).

The literature on carbamazepine and lactation encompasses 144 mother-infant pairs (Antonucci *et al.* 2018; Birnbaum *et al.* 2020; Brent and Wisner 1998; Frey *et al.* 1990, 2002; Froescher *et al.* 1984a; Kacirova *et al.* 2021b;

Kaneko *et al.* 1982; Kok *et al.* 1982; Kuhnz *et al.* 1983; Merlob *et al.* 1992; Niebyl *et al.* 1979; Pynnonen and Sillanpaa 1975; Pynnonen *et al.* 1977; Wisner and Perel 1998). Adverse events were reported in 9 (6.3%) children, including irritability (Kok *et al.* 1982), "hyperexcitable" presentation (Kuhnz *et al.* 1983), cholestatic hepatitis (Frey *et al.* 1990, 2002), poor nursing effort (Froescher *et al.* 1984a), increased serum concentration of g-glutamyl transpeptidase but no overt clinical sequelae (Merlob *et al.* 1992), "seizurelike" phenomenon (Brent and Wisner 1998), and recurrent regurgitation and vomiting (Antonucci *et al.* 2018). Serum carbamazepine concentrations range from undetectable to 65% of the maternal level (Birnbaum *et al.* 2020; Brent and Wisner 1998; Kacirova *et al.* 2021b; Kok *et al.* 1982; Merlob *et al.* 1992; Pynnonen and Sillanpaa 1975; Pynnonen *et al.* 1977; Wisner and Perel 1998). No adverse effects on cognitive functions at 3 (Meador *et al.* 2010) or 6 years of age (Meador *et al.* 2014) were observed in children exposed through breast milk.

Although the risks associated with prenatal carbamazepine exposure are better than those for valproate, clinical recommendations are similar. Carbamazepine should be avoided in pregnancy, especially during the first trimester. Folate supplementation (4-5 mg/day) is recommended throughout the reproductive years because of the high prevalence of unintended pregnancies. Prenatal surveillance for congenital abnormalities includes maternal serum alpha-fetoprotein, fetal echocardiography, and a level 2 ultrasound at approximately 16-18 weeks' gestation. Reports of hepatic dysfunction in nursing infants raise concern; thus, periodic assays of blood counts and serum liver enzymes of nursing infants are recommended.

Other Antiepileptic Drugs

Several other antiepileptic drugs are often used as off-label treatments for bipolar disorder, despite the lack of evidence supporting their efficacy. In the absence of efficacy, these agents should not be used to manage bipolar disorder in women of childbearing

age. However, because they are often inadvisably used for this purpose, a brief summary of their reproductive safety data is provided.

Oxcarbazepine

Reproductive safety data for oxcarbazepine are limited. A 2016 meta-analysis (Weston *et al.* 2016) found that the risk of major malformations associated with oxcarbazepine exposure is not different from that of the general population (2.39%). Another meta-analysis (Veroniki *et al.* 2017b) reported an increased risk for autism spectrum disorder (OR = 13.51; 95% CI, 1.28-221.40) among children exposed to oxcarbazepine during pregnancy; however, the wide confidence interval suggests caution in interpreting these results. A recent U.S. cohort study did not show increased risk of ischemic placental disease, preterm birth, or small-for-gestational-age birth among 1,109 infants from oxcarbazepine-exposed pregnancies (J. M. Cohen *et al.* 2019). Serum levels in nursing infants (*n* = 8) have to date been reported as undetectable, with no adverse effects noted (Birnbaum *et al.* 2020).

Topiramate

A 2016 meta-analysis (Weston *et al.* 2016) of prenatal topiramate exposure found a fourfold increase in the risk for major malformations among 359 exposed infants. A subsequent study (*N* = 2,425) observed increased risk for oral clefts (OR = 2.9), with a fivefold increase for daily dosages exceeding 100 mg (Hernandez-Diaz *et al.* 2018). Obstetrical outcome data have been more favorable, with a recent U.S. cohort study (*n* = 2,280) finding no association with risk of ischemic placental disease, preterm birth, or small-for-gestational-age birth (J. M. Cohen *et al.* 2019). Topiramate concentrations in 19 topiramate-exposed neonates were 51% of maternal levels (Kacirova *et al.* 2021a). Plasma levels in nursing infants were all undetectable in a recent study of topiramate in lactation (Birnbaum *et al.* 2020). Another study reported one adverse event, diarrhea, in 7 infants exposed to topiramate via breast milk (Westergren *et al.* 2014).

Gabapentin

A U.S. cohort study using a Medicaid database reported an increased risk for cardiac malformation (OR = 1.40) but no difference in overall malformation rates among gabapentin-exposed children (Patorno *et al.*

2020). The same study reported increased rates of preterm birth (OR = 1.28), small-for-gestational-age birth (OR = 1.17), and neonatal intensive care unit (NICU) admission (OR = 1.35) in association with gabapentin exposure. No adverse effects were reported among 8 infants exposed to gabapentin during lactation (Birnbaum *et al.* 2020).

Antipsychotics

Second-Generation A5ntipsychotics

The second-generation antipsychotics (SGAs) have emerged as first-line agents for psychotic disorders and are often used for other psychiatric indications, including bipolar disorder, anxiety disorders, and treatment-resistant depression. Although perinatal use of SGAs is rapidly expanding, the reproductive safety database is lagging. Findings from recent studies, albeit limited, are reassuring and suggest that SGAs may not be major teratogens (L. S. Cohen *et al.* 2016; Coughlin *et al.* 2015; Ellfolk *et al.* 2021; Huybrechts *et al.* 2016; Viguera *et al.* 2021). A neurodevelopmental study reported a transient delay in cognitive, motor, social-emotional, and adaptive behavior in SGA-exposed infants that resolved by 12 months of age (Peng *et al.* 2013). A recent population-based cohort study did not find an elevated risk of autism spectrum disorder or ADHD in association with prenatal SGA exposure (Wang *et al.* 2021).

Some studies have linked prenatal SGA use with adverse obstetrical outcomes including preterm delivery (Coughlin *et al.* 2015; Sadowski *et al.* 2013) and poor neonatal adaptation (Habermann *et al.* 2013; Sadowski *et al.* 2013), although others have not (Vigod *et al.* 2015; Wang *et al.* 2021). The metabolic side effects associated with SGAs warrant concern for gestational diabetes mellitus; however, a recent systematic review that included 10 studies found no association between prenatal SGA therapy, considered collectively, and gestational diabetes mellitus (Uguz 2019).

Clozapine

Reproductive safety data for clozapine, the oldest SGA, are limited primarily to case reports, case series, and small case-control studies (Thanigaivel *et al.* 2022). Anecdotal reports of minor anomalies include cephalohematoma, hyperpigmentation folds, and a coccygeal dimple (Stoner *et al.* 1997); delayed peristalsis (Moreno-Bruna *et al.* 2012); transient low-grade fever in an infant also exposed to lithium (Stoner *et al.* 1997); and poor muscle tone in a neonate also exposed to lorazepam (Di Michele *et al.* 1996). In a review of 61 children exposed to clozapine and other psychotropics, Dev and Krupp (1995) reported 5 children with congenital malformations and 5 with neonatal complications. In contrast, a review encompassing 620 children with prenatal clozapine exposure found no specific pattern of congenital malformations (Mehta and Van Lieshout 2017). A study of neurodevelopmental sequelae reported a higher rate of delayed development at 2 months and 6 months of age that resolved by 12 months among clozapine-exposed infants in comparison to those exposed to other SGAs (Shao *et al.* 2015).

A recent study using data from VigiBase, the world's largest pharmacovigilance database, found no evidence of poorer obstetrical outcomes when comparing clozapine exposure to other antipsychotics (Beex-Oosterhuis *et al.* 2020). However, other reports have linked clozapine with maternal gestational diabetes (Ellfolk *et al.* 2020; Galbally *et al.* 2020).

A recent investigation reported only partial placental transfer of clozapine ($n = 4$), with no evidence of accumulation during breastfeeding in the first 33 neonatal hours ($n = 1$) (Imaz *et al.* 2018). This finding is in contrast to a single case report describing similar medication concentrations in maternal serum and amniotic fluid but markedly higher concentrations in fetal serum and breast milk (Barnas *et al.* 1994), leading the authors to conclude that clozapine accumulates in the fetal circulation and breast milk. Although only one case of agranulocytosis has been reported in a clozapine-exposed infant, this potential risk and the requisite laboratory monitoring limit clozapine's perinatal utility (Dev and Krupp 1995; Uguz 2016).

Quetiapine

Reproductive safety studies for quetiapine, one of the more frequently prescribed SGAs during pregnancy (Halfdanarson *et al.* 2017; Moreno-Bruna *et al.* 2012), are outpacing other SGAs with largely reassuring findings. Specifically, two cohort studies from a nationwide Medicaid database (*n* = 4,221) (Huybrechts *et al.* 2016) and a national registry (*n* = 155) (L. S. Cohen *et al.* 2016, 2018) found no evidence linking quetiapine exposure with cardiac or other malformations. Data regarding the neurodevelopmental effects of quetiapine exposure are limited to one case report in which an infant was reported to exhibit normal development at 4.5 months of age (Lee *et al.* 2004).

In the Newport *et al.* (2007a) study of antipsychotic placental passage, quetiapine concentrations among neonates (*n* = 21) were 23% of maternal concentrations, the lowest placental passage rate among psychotropics studied to date.

Twelve cases of quetiapine use during lactation estimated the nursing infant dosage at 0.02%-0.43% of the weight-adjusted maternal daily dosage, with no adverse effects reported among the exposed infants (Aydin *et al.* 2015; Lee *et al.* 2004; Rampono *et al.* 2007; Yazdani-Brojeni *et al.* 2018).

Olanzapine

In a published birth registry from the Lilly Worldwide Pharmacovigilance Safety Database, 610 prospectively identified pregnancies exposed to olanzapine resulted in 9.8% premature births, 9.3% spontaneous abortions, 8% perinatal conditions, and 4.4% congenital anomalies (Brunner *et al.* 2013). A prospective study comparing outcomes among 151 pregnant women with SGA exposure (olanzapine, *n* = 0) to 151 pregnant control subjects reported no differences in rates of spontaneous abortion, stillbirth, major malformations, prematurity, or low birthweight (McKenna *et al.* 2005). In this study, one child exposed to an SGA (olanzapine) was observed to have major malformations (a series of midline defects including an oral cleft, encephalocele, and aqueductal stenosis). A meta-analysis reported a malformation rate of 3.5% among 1,090 olanzapine-exposed infants, comparing favorably to other SGAs (Ennis and Damkier 2015). In a large cohort study of Medicaid-insured women, olanzapine exposure during the first trimester (*n* = 1,394) did not significantly elevate the risk of major congenital or cardiac malformations when compared to unexposed pregnancies (Huybrechts *et al.* 2016).

In a study of antipsychotic placental passage rates and neonatal outcomes (Newport *et al.* 2007a), umbilical cord concentrations in olanzapine-exposed neonates (*n* = 4) were 72.1% of maternal concentrations.

Case reports of 41 infants exposed to olanzapine during lactation with no evidence of infant toxicity currently appear in the literature (Croke *et al.* 2002; Friedman and Rosenthal 2003; Gardiner *et al.* 2003; Gilad *et al.* 2011; Goldstein *et al.* 2000; Kirchheiner *et al.* 2000; Stiegler *et al.* 2014; Whitworth *et al.* 2010). The Lilly Safety Database reported on 62 breastfeeding mother-infant dyads with a 15.6% rate of adverse events, identified as somnolence, irritability, tremors, and insomnia (Brunner *et al.* 2013). Pharmacokinetic studies of olanzapine exposure during lactation have reported that plasma concentrations were undetectable in infants during nursing (Gardiner *et al.* 2003; Kirchheiner *et al.* 2000; Stiegler *et al.* 2014) and that the median infant daily dosage via breastfeeding was approximately 0.74%-1.8% of the maternal dosage (Ambresin *et al.* 2004; Aydin *et al.* 2015; Brunner *et al.* 2013; Croke *et al.* 2002; Gardiner *et al.* 2003).

Risperidone and Paliperidone

A meta-analysis reported a 5.1% malformation rate among 432 risperidone-exposed infants (Ennis and Damkier 2015). Another study of pregnancy outcomes for several SGAs (McKenna *et al.* 2005) reported no major malformations among 49 risperidone-exposed infants. In contrast, a cohort study of Medicaid-insured women indicated that risperidone exposure (*n* = 1,566) may carry a small risk for congenital malformations (OR = 1.26), which was not seen for other antipsychotics in the study (Huybrechts *et al.* 2016). A lone case report of paliperidone palmitate, the long-acting injectable formulation of paliperidone, reported no adverse obstetrical outcome (Ozdemir *et al.* 2015). There are no available data on the neurodevelopmental effects of risperidone or paliperidone exposure.

Pharmacokinetic studies have reported placental passage concentrations among neonates (*n* = 6) of 49.2% (Newport *et al.* 2007a), milk-to-plasma ratios of less than 0.5 for risperidone and less than 0.88 for paliperidone (Hill *et al.* 2000; Ilett *et al.* 2004; Weggelaar *et al.* 2011), and RIDs via lactation ranging from 2.3% to 4.7% of the maternal dose (Ilett *et al.* 2004; Weggelaar *et al.* 2011).

Aripiprazole

Prenatal use of aripiprazole, like that of quetiapine, is rising (Huybrechts *et al.* 2016; Park *et al.* 2017). Reproductive safety data for aripiprazole include findings from a large cohort study of 1,756 cases of first-trimester aripiprazole exposure, which reported no evidence of elevated risk for overall congenital or cardiac anomalies (Huybrechts *et al.* 2016). Similarly, prospective data from a national registry (*n* = 163) did not suggest an elevated risk for major malformations after aripiprazole exposure (Freeman *et al.* 2021). There has been no systematic study of neurodevelopmental outcomes following aripiprazole exposure.

Studies have raised concern about the impact of aripiprazole on obstetrical outcomes. For example, a prospective case series of 86 mother-infant dyads demonstrated an increased risk of preterm birth and fetal growth restriction but no evidence of increased risk for miscarriage, preeclampsia, or gestational diabetes (Bellet *et al.* 2015). Additionally, a retrospective case series of 26 prenatal aripiprazole exposures reported higher rates of gestational hypertension (*n* = 4) and NICU admission (*n* = 9) (Galbally *et al.* 2018). A single case report found poor respiratory effort at birth (Watanabe *et al.* 2011), but other case reports found no adverse obstetrical or neonatal outcomes (Gentile *et al.* 2011; Lutz *et al.* 2010; Windhager *et al.* 2014). In the only report of prenatal use of long-acting injectable aripiprazole, no pregnancy complications, congenital malformations, or developmental abnormalities were reported (Ballester-Gracia *et al.* 2019).

Pharmacokinetic studies found that aripiprazole's placental passage rate among four mother-infant dyads was 53.3%-54.7% (Watanabe *et al.* 2011; Windhager *et al.* 2014).

Of the three case reports of aripiprazole in lactation, the milk excretion profiles are questionable in two (Lutz *et al.* 2010; Schlotterbeck *et al.* 2007), and the other shows a 0.20 infant-to-maternal plasma ratio (Watanabe *et al.* 2011). Of note, aripiprazole has been linked with lactation failure, which may be due to its established prolactin-lowering effects (Cuomo *et al.* 2018; Komaroff 2021; Yskes *et al.* 2018).

Ziprasidone

The largest cohort study of prenatal ziprasidone exposure (*n* = 697) found no association with risk for overall or cardiac malformations (Huybrechts *et al.* 2016). Additionally, a single case report of ziprasidone exposure in utero and during breastfeeding reported normal growth and development at 6 months (Werremeyer 2009). Data concerning ziprasidone concentration in breast milk are limited to a single case that reported a milk-to-plasma ratio of 0.06 (Schlotterbeck *et al.* 2009).

Other SGAs

A case report of a single mother-infant breastfeeding dyad found a RID of 0.16% for lurasidone, with no adverse effects noted in the infant (Keightley *et al.* 2020). Otherwise, information about the perinatal use of other SGAs, including asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, and lurasidone, is scant.

First-Generation Antipsychotics

In contrast to SGAs, the first-generation antipsychotics (FGAs) have an extensive reproductive safety database addressing both somatic and neurobehavioral teratogenicity. Furthermore, the historical use of phenothiazine antipsychotics to treat nausea and vomiting of pregnancy aids in separating the effects of psychiatric illness and antipsychotic exposure on pregnancy outcome. Chlorpromazine, haloperidol, and perphenazine have received the greatest scrutiny, with no significant associations between these compounds and major malformations (Goldberg and DiMascio 1978; Hill and Stern 1979; Nurnberg and Prudic 1984). In a study of 100 women treated with haloperidol (mean dosage = 1.2 mg/day) for hyperemesis gravidarum, no differences in gestational duration, fetal viability, or birthweight were noted (Van Waes and Van de Velde 1969). In a prospective study encompassing nearly 20,000 women treated primarily with phenothiazines for emesis, Milkovich and van den Berg (1976) found no significant association with neonatal survival rates or severe anomalies. Similar results have been obtained in retrospective studies of women treated with trifluoperazine (Moriarty and Nance 1963; Rawlings *et al.* 1963). In contrast, Rumeau-Rouquette *et al.* (1977) reported a significant association of major anomalies with prenatal exposure to aliphatic phenothiazines but not piperazine-or piperidine-class agents. Reanalysis of the Milkovich and van den Berg (1976) data found a significant risk of malformations associated with phenothiazine exposure in weeks 4 through 10 of gestation (Edlund and Craig 1984). More recent data suggest that FGAs are not major teratogens (Huybrechts *et al.* 2016).

Neurobehavioral outcome studies encompassing 203 children with prenatal FGA exposure detected no significant differences in IQ scores at 4 years of age (Kris 1965; Slone *et al.* 1977), although low antipsychotic dosages were used by many women. Conversely, some laboratory animal studies (Hoffeld *et al.* 1968; Ordy *et al.* 1966; Robertson *et al.* 1980), although not all (Dallemagne and Weiss 1982), have demonstrated persistent deficits in learning and memory among offspring prenatally exposed to FGA medications.

Beyond the teratogenic potential of the FGAs lies the possibility of fetal and infant toxicities such as neuroleptic malignant syndrome (James 1988) and extrapyramidal side effects (EPS) manifested by heightened muscle tone and increased rooting and tendon reflexes persisting for several months

(Cleary 1977; Hill *et al.* 1966; O'Connor *et al.* 1981). Furthermore, prenatal exposure to FGAs has been associated with neonatal jaundice (Scokel and Jones 1962) and postnatal intestinal obstruction (Falterman and Richardson 1980).

In our study of antipsychotic placental passage, neonatal haloperidol (n = 13) concentrations were 66% of maternal concentrations (Newport *et al.* 2007a).

In lactation, chlorpromazine is the most widely studied typical antipsychotic, with 7 infants exposed to chlorpromazine during nursing exhibiting no developmental deficits at 16-month and 5-year follow-up evaluations (Kris and Carmichael 1957). However, 3 infants in another study whose mothers were prescribed both chlorpromazine and haloperidol exhibited evidence of developmental delay at 12-18 months (Yoshida *et al.* 1998b). Pharmacokinetic investigations of FGAs during lactation, including haloperidol (Stewart *et al.* 1980; Whalley *et al.* 1981; Yoshida *et al.* 1998b), trifluoperazine (Wilson *et al.* 1980; Yoshida *et al.* 1998b), perphenazine (Wilson *et al.* 1980), thioxanthenes (Matheson and Skjaeraasen 1988), and chlorpromazine (Yoshida *et al.* 1998b), have uniformly reported milk-to-plasma ratios of less than 1, although adequate control for distribution and time gradients is lacking in these studies. One group postulated that the physicochemical properties of perphenazine could lead it to become "trapped" in breast milk (Wilson *et al.* 1980); however, this speculation is unconfirmed.

Fetal and infant exposure to any of the various agents available for the management of EPS (e.g., diphenhydramine, benztropine, amantadine) also raises concern. Early reports of first-trimester diphenhydramine exposure reported elevated rates of major and minor anomalies, including elevated risk of oral clefts (Miller 1991; Saxen 1974; Wisner and Perel 1988). However, a more recent epidemiological investigation did not find an association between diphenhydramine use in early pregnancy and oral clefts (Li *et al.* 2013), and diphenhydramine is routinely used during pregnancy without issue. Clinical studies of the teratogenic potential of benztropine and amantadine are lacking, although laboratory animal studies indicate that amantadine is associated with an elevated risk of congenital malformations (Hirsch and Swartz 1980). Perinatal toxicities, including neonatal intestinal obstruction after gestational exposure to benztropine (Falterman and Richardson 1980) and a possible neonatal diphenhydramine withdrawal syndrome manifested by tremulousness and diarrhea (Parkin 1974), also warrant concern.

In summary, FGAs have been widely used for more than 60 years, and the paucity of data linking these agents to either teratogenic or toxic effects suggests that their risks are minimal. In particular, piperazine phenothiazines (e.g., trifluoperazine, perphenazine) may have especially limited teratogenic potential (Rumeau-Rouquette *et al.* 1977). FGAs used during the peripartum should be kept at the lowest effective dosage to minimize the need for adjunctive medications to manage EPS and to decrease the risk of neonatal EPS.

Anxiolytics

Benzodiazepines

A recent meta-analysis of 32 studies estimated the worldwide prevalence of benzodiazepine use during pregnancy to be 1.9% (Bais *et al.* 2020). Although the earliest benzodiazepine teratogenicity studies reported an increased risk of oral clefts after diazepam exposure (Aarskog 1975; Saxen 1975; Saxen and Saxen 1975), later studies failed to confirm this association (Ban *et al.* 2014; Entman and Vaughn 1984; Rosenberg *et al.* 1983; Shiono and Mills 1984). A subsequent meta-analysis demonstrated that prenatal benzodiazepine exposure does confer an increased risk of oral cleft, although the absolute risk increased by only 0.01% (Altshuler *et al.* 1996). This conclusion is consistent with a later case-control study finding no difference in the rate of prenatal benzodiazepine exposure between more than 38,000 infants with congenital anomalies and nearly 23,000 control subjects (Eros *et al.* 2002). Prospective studies of first-trimester alprazolam exposure encompassing approximately

1,300 pregnancies demonstrated no excess of oral clefts or other birth defects (Barry and St Clair 1987; Schick-Boschetto and Zuber 1992; St Clair and Schirmer 1992), and a study of first-trimester exposure to diazepam and temazepam echoed this finding (Ban *et al.* 2014). A large well-designed cohort study found no increased risk of congenital malformations with benzodiazepine or hypnotic benzodiazepine receptor agonists after excluding concomitant drug exposures (Wikner *et al.* 2007). A recent meta-analysis of eight prospective cohort studies reported no increased risk of major malformations with benzodiazepine exposure alone but found an increased risk of malformations with a combination of benzodiazepines and antidepressants (Grigoriadis *et al.* 2019). Data from a recent large multisite population-based case-control study suggested increased risks with prenatal benzodiazepine exposure for specific anomalies including Dandy-Walker malformation, anophthalmia and microphthalmia, esophageal atresia or stenosis, and pulmonary valve stenosis; however, given small sample sizes and wide confidence intervals, replication of these data is needed (Tinker *et al.* 2019).

Although benzodiazepine teratogenicity data are somewhat mixed, benzodiazepine neonatal syndromes are well documented. Numerous groups have described a floppy infant syndrome characterized by hypothermia, lethargy, poor respiratory effort, and feeding difficulties following benzodiazepine exposure in late pregnancy (Erkkola *et al.* 1983; Fisher *et al.* 1985; Haram 1977; Kallen and Reis 2012; Kriel and Cloyd 1982; McAuley *et al.* 1982; Sanchis *et al.* 1991; Speight 1977; Woods and Malan 1978). In a study of 53 infants, lorazepam-exposed term neonates showed no evidence of toxicity other than a brief delay in establishing feeding, whereas preterm infants and term infants whose mothers had received larger intravenous dosages of lorazepam exhibited symptoms consistent with floppy infant syndrome (Whitelaw *et al.* 1981). Neonatal withdrawal syndromes characterized by restlessness, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea, and vomiting are described in infants whose mothers were taking alprazolam (Barry and St Clair 1987), chlordiazepoxide (Athinarayanan *et al.* 1976; Bitnum 1969; Stirrat *et al.* 1974), and diazepam (Backes and Cordero 1980; Mazzi 1977). More recent studies have suggested that benzodiazepine use in pregnancy may be associated with poor neonatal outcomes, including preterm delivery, low birthweight, smaller head circumference, low Apgar scores, neonatal adaptation syndrome, NICU admission, and respiratory distress; however, concomitant antidepressant use and issues of confounding complicate these findings (Calderon-Margalit *et al.* 2009; Freeman *et al.* 2018; Huitfeldt *et al.* 2020; Salisbury *et al.* 2016; Yonkers *et al.* 2017). Benzodiazepine neonatal syndromes have been reported to persist for as long as 3 months after delivery (for a review, see Miller 1991).

Pharmacokinetic studies during pregnancy indicate that benzodiazepines readily traverse the placenta and with prolonged administration may accumulate in the fetus (Mandelli *et al.* 1975; Shannon *et al.* 1972). For example, fetal concentrations of diazepam at delivery are typically higher than maternal concentrations (Erkkola *et al.* 1974). Because benzodiazepine metabolism in the fetus is slower than that in the adult, it is understandable that an agent such as diazepam, with multiple active metabolites, might accumulate in the fetus. In addition, high concentrations of diazepam are sequestered in lipophilic fetal tissues, such as the brain, lungs, and heart (Mandelli *et al.* 1975). In contrast, fetal/maternal ratios of lorazepam (which has no active metabolites) are typically less than 1 (Whitelaw *et al.* 1981). Yet neonatal clearance of lorazepam is slow, with detectable levels evident 8 days after delivery (Whitelaw *et al.* 1981), and the clearance of chlordiazepoxide appears to be even slower (Athinarayanan *et al.* 1976).

More studies to evaluate the neurobehavioral effects of prenatal benzodiazepine exposure are needed. A series of laboratory animal studies originally raised concerns that prenatal benzodiazepine exposure may produce deficits in memory and learning ability (Frieder *et al.* 1984; Hassmannova and Myslivecek 1994; Jaiswal and Bhattacharya 1993; Myslivecek *et al.* 1991). A benzodiazepine exposure syndrome--consisting of growth retardation, dysmorphism, and mental and psychomotor retardation in infants (Laegreid *et al.* 1987)--has been reported, but other investigators have disputed this finding (Winter *et al.* 1987). Some studies have found an increased risk for internalizing problems in children up to 3 years of age (Brandlistuen *et al.* 2017). However, more recent data have been reassuring, with multiple studies suggesting no adverse neurobehavioral effects with in utero benzodiazepine exposure at a variety of time points, including no differences in the incidence of behavioral abnormalities at age 8 months or in IQ scores at 4 years of age (Hartz *et al.* 1975), no correlation between antenatal exposure and language competence at age 3 years (Odsbu *et al.* 2015), no correlation with clinically relevant motor, communication, and ADHD disorders in preschoolers (Lupattelli *et al.* 2019), and no correlation with internalizing or externalizing symptoms at 5 and 6 years of age (Sundbakk *et al.* 2019; Radojcic *et al.* 2017).

Buist *et al.* (1990) concluded that benzodiazepines at low dosages present no contraindication to nursing. A retrospective cohort study found a sedation rate of 1.6% in infants exposed to benzodiazepines while breastfeeding, but there was no association with dosage (Kelly *et al.* 2012). However, infants with impaired metabolic capacity may exhibit sedation and poor feeding even with low maternal dosages (Wesson *et al.* 1985). Overall, benzodiazepines exhibit lower milk-to-plasma ratios than other classes of psychotropics. For example, Wretlind (1987) found a milk-to-plasma ratio of 0.1-0.3 for oxazepam and calculated that the infant daily dose via lactation is 1/1,000 of the maternal dose. The percentage of the maternal dose of lorazepam to which a nursing infant is exposed has been estimated to be 2.2% (Summerfield and Nielsen 1985). A recent study by Nishimura *et al.* (2021) found the RID for multiple benzodiazepines, including clonazepam, alprazolam, and lorazepam, to be less than 10%, with no report of adverse effects.

In summary, benzodiazepines do not appear to carry a significant risk of somatic teratogenesis, but neurobehavioral sequelae remain obscure. Because benzodiazepines are associated with neonatal risks, they should be used judiciously and tapered before delivery if possible. Benzodiazepines should not be abruptly withdrawn during pregnancy. Because lorazepam and oxazepam are less dependent on hepatic metabolism, they theoretically have less potential for fetal accumulation during pregnancy. Finally, benzodiazepines can be safely administered, in judicious dosages, during lactation. Consideration should be given to those with shorter half-lives (lorazepam) and lower lipid solubility (oxazepam) when possible. Breastfeeding should be discontinued if an infant exhibits sedation or other signs of benzodiazepine toxicity.

Buspirone

Buspirone has garnered a unique, and arguably illogical, position within the psychotropic armamentarium. Although reassuring results from animal studies led to a favorable FDA pregnancy designation for buspirone, published clinical data are limited to a single report of prenatal administration of buspirone ($n = 14$) identifying one infant born with a major malformation (Wilton *et al.* 1998). There are no published reports regarding buspirone during lactation.

Hydroxyzine

The antihistamine hydroxyzine is often used as an off-label as-needed treatment for anxiety, despite evidence challenging its efficacy when used in this manner (Papadopoulos *et al.* 2010). A cohort study examining various outcomes associated with hydroxyzine ($n = 53$) found no evidence linking it to major malformations, low birthweight, preterm birth, or neonatal distress (Einarson *et al.* 1997). However, a review of the French Pharmacovigilance Database discovered that hydroxyzine was the third most frequently cited medication associated with adverse effects in breastfeeding infants; complications included sedation, malaise, bradycardia, cyanosis, and constipation (Soussan *et al.* 2014). There are no reports regarding hydroxyzine's reproductive pharmacokinetics or neurodevelopmental consequences of exposure.

Psychostimulants

Methylphenidate and Amphetamines

The prevalence of ADHD among adult women is 3.2% (Kessler *et al.* 2006), and psychostimulants are the gold standard for treatment. Unfortunately, the reproductive safety data for these medications remain sparse. While there is compelling evidence that prenatal methamphetamine abuse conveys an increased risk of preeclampsia and hypertension, fetal demise, preterm delivery, and intrauterine growth restriction, not to mention the potential for long-term neurological, developmental, and behavioral problems in the baby (Dinger *et al.* 2017), it is problematic to draw inferences from methamphetamine abuse outcomes and apply them to therapeutic psychostimulant use, because illicit misuse is likely to involve much higher dosages than prescribed medication, and abuse of stimulants is also accompanied by use of other addictive substances, such as tobacco, alcohol, and other drugs, which can cloud the origin of a negative outcome (Debooy *et al.* 1993).

To date, the data regarding therapeutic use of psychostimulants during pregnancy, albeit limited, have been reassuring. Stimulants at prescribed dosages do not appear to show any increased risk of malformations (Diav-Citrin *et al.* 2016; Pottegard *et al.* 2014). Although one study showed a slightly higher rate of cardiac malformations, the difference was not statistically significant (Huybrechts *et al.* 2018). There are no systematic studies examining neurodevelopmental outcomes following prenatal psychostimulant therapy.

A Swedish study comparing nearly 1,600 stimulant-exposed babies with approximately 9,500 babies of women with untreated ADHD found slightly higher risks of preterm birth and NICU stay in association with psychostimulant therapy; however, this study found no differences in congenital malformations, Apgar scores, or neonatal withdrawal symptoms (Norby *et al.* 2017). In addition, a nested case-control study reported an increased risk for gestational hypertension (OR = 6.11) among women treated with psychostimulants; in the subgroup receiving stimulant therapy, those with gestational hypertension had higher daily stimulant dosages than those without hypertension (33.8 mg vs. 11.9 mg) (Newport *et al.* 2016).

Psychostimulants are not contraindicated in lactation. Reports have shown drug levels to be low or nondetectable in breast milk (Marchese *et al.* 2015; Ornoy 2018). Among the medications for which data are available, the RID is consistently below 10%, with methylphenidate-derived medications having lower RIDs than amphetamine-derived ones

(Hale 2021). In one study of 103 babies exposed to psychostimulants in breast milk, no adverse effects on the babies were noted (Ayd 1973). However, by virtue of their dopaminergic mechanism of action, and, in turn, dopamine's inhibitory impact on prolactin activity, stimulants can theoretically interfere with breast milk production, particularly at higher dosages (Drugs and Lactation Database 2023a). However, some studies have failed to find a statistically significant effect, and clinical experience varies among physicians.

Atomoxetine

While psychostimulant medications are generally the first-line choice for treatment of ADHD, there are also nonstimulant options, including atomoxetine, an SNRI. Few data are available on atomoxetine, but so far no risk for malformations or adverse pregnancy outcomes has been noted (J. M. Cohen *et al.* 2017). There are no published data on the neurodevelopmental effect of atomoxetine or the safety of atomoxetine in breastfeeding, but two case reports showed no complications in the infants (Drugs and Lactation Database 2023b).

Modafinil and Armodafinil

While they do not hold FDA indications for ADHD, the psychostimulants modafinil and armodafinil are sometimes used off-label for ADHD. Their reproductive safety data are scant and mixed thus far. In 2020, two small studies with sample sizes of 49 and 102, respectively, showed increased risk (12%-13%) of congenital malformations including hypospadias, torticollis, and heart defects (Damkier and Broe 2020; Kaplan *et al.* 2021), yet later that year a larger study of 133 exposed pregnancies showed no increased risk (Cesta *et al.* 2020). With so little information, we need to remain cautious about the use of these medications in pregnancy. The breastfeeding data are also very limited, with just one formal case report of a RID of 5.3% for a nursing mother receiving 250 mg of modafinil daily for hypersomnia (Aurora *et al.* 2018).

Anti-Addiction Medications

Substance use disorders convey a host of risks during pregnancy and the postpartum period. With the emergence of medication-assisted treatment (MAT) to aid the recovery

of those addicted to certain substances, particularly opioids, alcohol, and tobacco, using anti-addiction medicines during pregnancy warrants careful consideration. The risks of such agents must be weighed against the well-documented risks of continued substance abuse. For example, opioid abuse during pregnancy carries myriad risks including repeated episodes of fetal withdrawal, fetal seizures, diminished fetal growth, preterm birth, and fetal death (National Institute on Drug Abuse 2017). Approximately 10% of American women continue to consume alcohol during pregnancy, with roughly one-third of these binge drinking (Tan *et al.* 2015). Prenatal alcohol abuse is associated with a heightened risk of miscarriage, stillbirth, preterm birth, sudden infant death syndrome, and fetal alcohol spectrum disorder (National Institute on Alcohol Abuse and Alcoholism 2021). Tobacco use during pregnancy is linked to increased risk for miscarriage, stillbirth, preterm birth, low birthweight, and childhood asthma and vision problems (National Institute on Drug Abuse 2020).

Medications for Opioid Use Disorder

Opioid Agonists

MAT has emerged as the standard of care for opioid use disorder for all adults, including pregnant women. Opioid detoxification during pregnancy is not recommended because of high relapse rates coupled with the poor outcomes noted above among women who continue to abuse opioids. MAT for opioid abuse may consist of treatment with an opioid agonist, methadone or buprenorphine, or a long-acting injectable opioid antagonist, naltrexone.

Opioid-addicted pregnant women receiving methadone or buprenorphine MAT are more likely to engage in prenatal care and have reduced infection risk, normal fetal growth, and lower fetal and neonatal mortality than those without MAT (Jones *et al.* 2008; Zhao *et al.* 2020). Although a consensus has emerged that prenatal MAT is far safer than continued opioid abuse, it is not without risks. Several studies, though not all (Zedler *et al.* 2016), have reported higher malformation rates among methadone-exposed children, including a population-based study of overall malformation rates (OR = 2.05) (Wurst *et al.* 2016); a case-control study finding a higher risk for Pierre Robin sequence (OR = 12.3), a rare craniofacial anomaly, and cleft palate (OR = 5.0) (Cleary *et al.* 2020); and another reporting a higher malformation rate than among children exposed to naltrexone and buprenorphine (Kelty and Hulse 2017a). To date, studies have not demonstrated an association between prenatal buprenorphine exposure and risk for major malformations (Kelty and Hulse 2017b; Wurst *et al.* 2016; Zedler *et al.* 2016).

While there are obstetrical and newborn risks associated with any opioid agonist therapy, such as preterm birth, low birthweight, and neonatal opioid withdrawal syndrome (NOWS), continued opioid abuse leads to more frequent and more severe poor outcomes (Minozzi *et al.* 2020; Mozurkewich and Rayburn 2014; Tran *et al.* 2017). As mentioned, NOWS is an expected adverse outcome with opioid agonist therapy proximate to delivery. For example, the landmark Maternal Opioid Treatment: Human Experimental Research randomized clinical trial showed a similar incidence of NOWS among newborns of buprenorphine-and methadone-maintained mothers (Jones *et al.* 2010); however, although pregnant women receiving buprenorphine MAT were twice as likely to screen positive for continued illicit opioid use at delivery as those receiving methadone MAT (11.1% vs. 5.6%) (Kaltenbach *et al.* 2012), the severity of NOWS was markedly lower among infants exposed to buprenorphine than those exposed to methadone, resulting in a shorter duration of NOWS treatment (4.1 days vs. 9.9 days), a shorter hospital stay (10 days vs. 17.5 days), and a lower morphine requirement for neonatal detoxification (mean dosage 1.1 mg vs 10.4 mg) (Jones *et al.* 2010). Moreover, methadone, but not buprenorphine, has been associated with neonatal QTc prolongation and arrhythmias (Hussain and Ewer 2007; Parikh *et al.* 2011).

Serial assessments of cognitive and language development, temperament, and sensory processing through 3 years of age conducted by the Maternal Opioid Treatment: Human Experimental Research study (Kaltenbach *et al.* 2018) demonstrated no deleterious effect of prenatal MAT with methadone or buprenorphine.

The American College of Obstetricians and Gynecologists encourages new mothers who are stable on opioid agonist therapy and abstinent from illicit opioid use to breastfeed in the absence of other contraindications such as maternal HIV infection (American College of Obstetricians and Gynecologists 2017). A study of seven breastfeeding infants demonstrated no adverse effects of buprenorphine exposure, with median milk/plasma ratios of 1.7 and 0.7 and RIDs of 0.2% and 0.12% for buprenorphine and its active metabolite norbuprenorphine, respectively (Lindemalm *et al.* 2009). A methadone lactation study ($n = 20$) revealed a mean milk/plasma ratio of 0.40 and a RID of 2.1% (Bogen *et al.* 2011).

A systematic review of eight studies examining NOWS concluded that breastfeeding reduced the severity and duration of NOWS for infants of women receiving methadone but not buprenorphine MAT (McQueen *et al.* 2019). However, in light of methadone's low RID via lactation, it seems unlikely that extending methadone exposure during breastfeeding alone explains the attenuation of NOWS. It has been suggested that this may instead be a consequence of physical contact between mother and newborn when breastfeeding, as well as maternal engagement in care (Saia *et al.* 2016).

Of note, one key advantage for buprenorphine over methadone is its accessibility. Methadone maintenance requires clinic attendance 6 or 7 days per week, and take-home doses are seldom permitted. The difficulties this produces for pregnant and postpartum women has led one group to recommend greater flexibility in methadone maintenance delivery for pregnant and postpartum women (McCarthy *et al.* 2021).

Opioid Antagonists

Introduced for the treatment of opioid use disorders as a long-acting injectable formulation, the opioid antagonist naltrexone later garnered an FDA indication as an oral formulation for the treatment of alcohol use disorder. Because of its limited reproductive safety data relative to methadone and buprenorphine, naltrexone is less preferred for managing opioid abuse during pregnancy (Ecker *et al.* 2019). A cohort study comparing 121 naltrexone-treated and 109 methadone-or buprenorphine-treated pregnant women observed no difference in rates of congenital malformation (Towers *et al.* 2020). To date, there are no clinical studies examining the neurodevelopmental sequelae of prenatal naltrexone exposure.

Although some have expressed concern about the risk of fetal abstinence syndrome during the initiation of prenatal naltrexone treatment and the risk for opioid relapse during the required 7-10 days of opioid abstinence following detoxification (Kelty and Hulse 2017a; Minozzi *et al.* 2011), these concerns were not realized in a recent prospective study (Towers *et al.* 2020). Conversely, two studies indicate that prenatal MAT with naltrexone, in comparison to the opioid agonists, carries a significantly lower risk of NOWS and shorter length of hospitalization (Towers *et al.* 2020; Wachman *et al.* 2019).

The lone in vivo study of naltrexone placental passage ($n = 20$) observed mean umbilical cord/maternal plasma ratios of 74% and 92%, respectively, for naltrexone and its active metabolite 6-b-naltrexol (Towers *et al.* 2020). Naltrexone therapy proximate to delivery poses a challenge for postdelivery pain management (Jones and Terplan 2018). However, both maternal and fetal concentrations were undetectable at delivery when oral naltrexone had been discontinued at least 60 hours before delivery (Towers *et al.* 2020), suggesting that postdelivery pain management concerns can be remedied by discontinuing naltrexone therapy as little as 3 days before delivery. If the long-acting injectable is continued during pregnancy, it is recommended to transition to the oral formulation at least 1 month before the expected delivery.

Naltrexone use during breastfeeding is limited to one case report, where the total RID (naltrexone + 6-b-naltrexol) was estimated to be 1.06% (Chan *et al.* 2004).

The other commercially available opioid antagonist, naloxone, is administered parenterally as an antidote for opioid overdose. Little guidance is available on naloxone use during gestation. A general recommendation for any patient who has overdosed on an opioid is to administer naloxone when the respiratory rate drops to 12 or below (Blandthorn *et al.* 2018). To minimize the potential for maternal and fetal opioid withdrawal after naloxone administration, treatment should be initiated with the lowest dosage of naloxone and accompanied by medical care to monitor both the mother and fetus (Blandthorn *et al.* 2018).

Medications for Alcohol Use Disorder

Medications available for the management of alcohol use disorder include naltrexone, acamprosate, disulfiram, and two additional medications approved for use in Europe, nalmefene and gamma-hydroxybutyrate. Reproductive safety data for all these agents remains sparse; consequently, their use during pregnancy, despite the attendant risks of prenatal alcohol abuse, is not routinely encouraged (Reus *et al.* 2018; Rolland *et al.* 2016; Thibaut *et al.* 2019). Some guidelines suggest that first-line maintenance agents for alcoholism (i.e., naltrexone or acamprosate) be considered on a case-by-case basis for women who are stable on the medication before conception (Reus *et al.* 2018; Rolland *et al.* 2016).

Acamprosate

The reproductive safety data for naltrexone were reviewed earlier (see "Opioid Antagonists" in the "Medications for Opioid Use Disorder" section). Acamprosate's reproductive safety data are limited to a single retrospective cohort study (Kelty *et al.* 2019) reporting that prenatal acamprosate (n = 54) exposure was not associated with heightened risk for congenital malformations, low birthweight, or neonatal complications. There are no acamprosate studies examining the neurodevelopmental effects of prenatal exposure or its safety profile in lactation.

Disulfiram

The extant reproductive safety literature for disulfiram encompasses 38 cases, of which 11 (28.9%) reported a major malformation; however, many of the fetuses were also exposed to alcohol and other potentially causative substances (Kelty *et al.* 2021). Theoretical concerns about the impact of the "Antabuse reaction" on the fetus led the French Alcohol Society guideline to recommend discontinuing disulfiram therapy during pregnancy even if the patient is stabilized on it before conception (Rolland *et al.* 2016).

Medications for Smoking Cessation

Pregnancy often serves as a motivating factor for smoking cessation; however, many women may need pharmacological assistance (American College of Obstetricians and Gynecologists 2020; Myung *et al.* 2012). The mainstays of smoking cessation pharmacotherapies in the United States include bupropion, varenicline, and nicotine replacement therapy (NRT). Although it has been challenging to distinguish the effects of NRT from those of continued smoking, NRT products are not thought to be major teratogens; however, evidence for other perinatal outcomes is inconclusive (Blanc *et al.* 2021; Taylor *et al.* 2021). Two recent systematic reviews (Patnode *et al.* 2021; Taylor *et al.* 2021) did not find a relationship between NRT and either positive or adverse perinatal outcomes. Another systematic review (Blanc *et al.* 2021) reported an association between NRT during pregnancy and infant colic at 6 months and risk of ADHD at age 7 years, with ORs similar to those with continued tobacco use. Similarly, rates of stillbirth, adverse birth outcomes, or congenital malformations following prenatal exposure to NRT, bupropion, or varenicline did not differ from those among infants whose mothers continued to smoke but were unexposed to these medications (Patnode *et al.* 2021). In a recent meta-analysis, bupropion, used as a smoking cessation aid, did not have any positive or negative effects on rates of major malformations, birthweight, or premature birth (Turner *et al.* 2019). Data are sparse for varenicline use in pregnancy, but the limited available data do not suggest it is a major teratogen (Turner *et al.* 2019). Despite the limited and sometimes conflicting safety data regarding the use of NRT, bupropion, or varenicline during pregnancy, the American College of Obstetricians and Gynecologists still recommends offering them as possible smoking cessation aids (American College of Obstetricians and Gynecologists 2020).

Unfortunately, more than half of women who abstain from using tobacco during pregnancy resume smoking within 6-12 months postpartum (American College of Obstetricians and Gynecologists 2020; Napierala *et al.* 2016). Data are limited regarding the risks of NRT during lactation, but it is well known that nicotine passes freely into breast milk. In a study of 15 lactating women smoking an average of 17 cigarettes a day, the nicotine levels for the 21 mg patch were similar to their levels when smoking but declined by almost 70% with the 7 mg patch (Ilett *et al.* 2003). The authors estimated that the RID of the nicotine patches was approximately 1.9% (Ilett *et al.* 2003). There are no known studies with other NRT formulations, such as lozenges or gum. Maternal smoking has been associated with decreased milk production and elevated risk of sudden infant death syndrome, with nicotine itself being the suspected cause (Taylor *et al.* 2021). This implies that NRT products may have similar risks, although data supporting this theory are lacking. Data for bupropion during lactation are limited, but reported concentrations are low and unlikely to result in negative outcomes. The use of varenicline during lactation is not currently recommended because of the lack of published data (American College of Obstetricians and Gynecologists 2020).

Hypnotics

Insomnia commonly co-occurs with various mental disorders during pregnancy and the postpartum period; moreover, the severity of prenatal depression and anxiety is associated with the frequency of hypnotic use during gestation (Newport *et al.* 2012). Consequently, the safety of hypnotic pharmacotherapy warrants discussion. Pharmacotherapy alternatives for insomnia include benzodiazepines (discussed previously), benzodiazepine receptor agonists, antihistamine hypnotics, melatonin receptor agonists, and "natural" hypnotics.

Benzodiazepine Receptor Agonists

The benzodiazepine receptor agonists, including zolpidem, zaleplon, and zopiclone and its enantiomer eszopiclone, have been widely used during pregnancy despite limited reproductive safety data. Although these limited data do not provide evidence, as yet, for increasing risk for congenital malformations, these medications have been associated with neonatal withdrawal (Ban *et al.* 2014; Wikner *et al.* 2007; Wilton *et al.* 1998).

Zolpidem crosses the placenta but rapidly clears the fetal circulation (Askew 2007; Juric *et al.* 2009). Small preliminary studies are not indicative of malformation risk (Juric *et al.* 2009; Wang *et al.* 2010), although one study reported a small increase in the risk for gastrointestinal tract malformations (Wikner and Kallen 2011). Data on the risk of preterm delivery and low birthweight associated with zolpidem use are mixed (Juric *et al.* 2009; Wang *et al.* 2010; Wikner *et al.* 2007). Limited data on zaleplon (n = 32) found no evidence of increased risk of malformations (Wikner and Kallen 2011). Two studies reported no increased rate of malformations or low birthweight with zopiclone (Diav-Citrin *et al.* 1999; Stephens *et al.* 2008). There are no published reports regarding the safety profile or pharmacokinetics of eszopiclone exposure during gestation.

The RID in maternal breast milk is 0.4% for zaleplon, 0.02%-0.18% for zolpidem, and 1.5% for zopiclone (Hale 2021). There are no published reports regarding eszopiclone during lactation, although its breast milk excretion rate and safety profile are presumably akin to those of the racemic mixture, zopiclone.

Antihistaminic Hypnotics

Diphenhydramine and Doxylamine

Meta-analyses have not found an association between first-generation antihistamines (e.g., diphenhydramine and doxylamine) as a class and malformation risk (McKeigue *et al.* 1994; Seto *et al.* 1997). The majority of available safety data come from two large case-control studies. An initial analysis of the National Birth Defects Prevention Study reported weak to moderate associations between diphenhydramine and doxylamine exposure and isolated noncardiac malformations (Gilboa *et al.* 2009); however, a subsequent analysis of the same data found no increase in risk for congenital malformations with these agents (Anderka *et al.* 2012). An analysis of the Slone Epidemiology Center Birth Defects Study found no increased risk of congenital malformations with diphenhydramine or doxylamine exposure (Li *et al.* 2013). One randomized controlled trial found diphenhydramine to be efficacious for insomnia in pregnancy (Khazaie *et al.* 2013).

Trazodone

Trazodone is a phenylpiperazine antidepressant most often used as a sleep aid because of its sedating properties. Literature on trazodone in pregnancy is limited. Two prospective controlled studies did not find an increased risk of congenital malformations (Einarson *et al.* 2003, 2009). Cord blood levels are equivalent to maternal serum levels (Saito *et al.* 2021). One study of excretion of trazodone into breast milk suggests low transmission, with infants receiving 0.6% of the maternal dose (Verbeeck *et al.* 1986). One randomized controlled trial found trazodone efficacious for insomnia in pregnancy, with increased sleep duration and efficiency (Khazaie *et al.* 2013).

Tricyclic Antidepressants

The potent antihistamines amitriptyline and nortriptyline are TCAs that may be used in the treatment of insomnia in pregnancy, in addition to depression and migraine prophylaxis. Earlier concerns regarding limb anomalies were not confirmed in subsequent studies (Altshuler *et al.* 1996; Vasilakis-Scaramozza *et al.* 2013), and neurodevelopmental data are generally reassuring (Nulman *et al.* 2002). Limited data on neonatal impacts at delivery suggest increased risk for tachycardia and withdrawal (Misri and

Sivertz 1991; ter Horst *et al.* 2012). The RID of amitriptyline in maternal milk has been estimated as 1.08%-2.8%, with one report of severe sedation and poor feeding in an exposed infant (Hale 2021; Uguz 2017). The RID of nortriptyline is 1.7%-3.36%, and there have been no reported infant concerns (Hale 2021).

Quetiapine

Quetiapine is an SGA that is often used at lower dosages as an off-label treatment for insomnia in pregnancy, given its sedative properties and favorable reproductive safety profile. Its safety profile was reviewed earlier in this chapter (see "Quetiapine" under "Second-Generation Antipsychotics").

Melatonin Receptor Agonists

Melatonin is a neuroendocrine hormone secreted by the pineal gland, which regulates multiple biological systems, including circadian rhythm, the endocrine system, and the immune system. Maternal melatonin crosses the placenta and enters the fetal circulation freely, where it regulates fetal circadian rhythm and reproductive development (Davis 1997). Although studies suggest that endogenous melatonin is essential for pregnancy, and perhaps even protective against preeclampsia and miscarriage (Tamura *et al.* 2008), there are no published reports of the safety of exogenous melatonin supplementation in pregnancy. Conflicting data from animal studies suggest possible risks of melatonin supplementation, including decreased birthweight, increased mortality, and effects on reproductive development (Colmenero *et al.* 1991; Gonzalez-Candia *et al.* 2016; Singh *et al.* 2012), contrasting possible neuroprotective benefits (Dominguez Rubio *et al.* 2017). Limited published data on endogenous melatonin levels in maternal breast milk suggest that the amount of melatonin in milk ranges from 35%-80% of maternal plasma levels (Illnerova *et al.* 1993), and there are no available data on levels of exogenous melatonin in maternal breast milk (Hale

2021). Melatonin supplementation is discouraged during pregnancy and lactation, given the concerning animal data, lack of human evidence, and theoretical risks.

Agomelatine is a melatonin receptor agonist that is available in Europe but not the United States. There are no published reports on the use of agomelatine in pregnancy; however, there are two case reports on its use in lactation, suggesting low levels in maternal breast milk and limited risk of exposure to the infant due to the short half-life (Schmidt *et al.* 2013; Xiao 2021).

There are no published reports on the use of melatonin receptor agonists ramelteon and tasimelteon in pregnancy or lactation.

Orexin Antagonists

The recently introduced orexin antagonists are a distinct class of hypnotic agents. Three orexin antagonists, daridorexant, lemborexant, and suvorexant, are currently approved for use in the United States. There are no published reports on the use of these agents during pregnancy or lactation.

Natural Hypnotics

Natural agents frequently used to treat insomnia include GABA, glycine, lavender, passionflower, L-theanine, L-tryptophan, magnesium, and valerian root. Most of these agents have no published reproductive safety data for pregnancy or lactation.

While there are no published reports on the use of lavender in pregnancy or lactation, its use for pain control during labor demonstrated significant therapeutic effects for the mother, with no evident adverse neonatal effects (Yazdkhasti and Pirak 2016). There are no published reports on the use of GABA in human pregnancy or lactation; however, animal data suggest that early pregnancy exposure to GABA may impair endometrial receptivity and embryo development in rats (Tian *et al.* 2020).

Passionflower (*Passiflora incarnata*), an herbal supplement used for anxiety and insomnia, has been associated with neonatal death, premature rupture of membranes, meconium aspiration, and persistent pulmonary hypertension of the newborn in one case report series (Ozturk and Kalayci 2018).

The reproductive safety of L-tryptophan, an amino acid used for depression and insomnia, has received limited scrutiny. One study reported a significant decrease in fetal breathing movements associated with tryptophan exposure (Devoe *et al.* 1986). There are no published data on L-tryptophan in lactation; however, given the high dosages needed, high maternal plasma levels, and frequent report of adverse effects, use in lactation cannot be recommended (Pizzorno and Murray 2020).

Magnesium is an essential mineral often taken as an oral dietary supplement for leg cramps, anxiety, and insomnia. Guidelines produced by the Institutes of Medicine suggest daily dosages below the upper limit of 350 mg daily (Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1997). It has also been examined for benefit in the context of a variety of maternal and neonatal obstetrical outcomes; however, a systematic review found no high-quality evidence to support magnesium oral supplementation in pregnancy (Makrides *et al.* 2014). The authors found no significant difference in primary outcomes of perinatal mortality, small-for-gestational-age status, maternal mortality, and preeclampsia. They attributed a slightly increased risk of neonatal death in the supplemented group to a series of anomalous severe congenital abnormalities.

Conclusion: Clinical Decision-Making During the Perinatal Period

When managing psychiatric illness during pregnancy or breastfeeding, simply ingesting the minutiae of the reproductive safety literature pertinent to each medication is insufficient for providing optimal care. Although this fund of knowledge is necessary, it must be interfaced with a sound framework for choosing between the various available treatment alternatives. Fundamental to this process is recognizing that the selection must consider the risks to mother, unborn child, and even older children attributable to the illness and weigh those against risks posed by psychotropic exposure. Ultimately, no risk-free alternative exists other than choosing not to conceive. Thus, there are numerous overarching concerns to be confronted when any pharmacotherapy is under consideration. These concerns form the basis for delineating general principles to guide perinatal psychiatric treatment planning, which are perhaps best conveyed through a series of questions commonly encountered during the decision-making process.

Is It Safe to Take This Medication While Pregnant (or Breastfeeding)?

Patients, and many clinicians, often try to limit the risk assessment to this sole question, seeking an answer devoid of ambiguity. However, any decision predicated solely on this question is wholly inadequate. First, this question ignores the risk posed by the illness. Second, there is no psychotropic medication for which all potential risks have been exhaustively examined and dismissed. Consequently, no psychotropic can be categorically deemed safe during pregnancy or lactation. Third, posed in this manner, the question inexorably leads to an assumption that maternal well-being is always in direct competition with fetal well-being. This so-called fetal-maternal conflict should be avoided, as it is a sure path to self-recrimination for any expectant mother faced with the challenges posed by perinatal mental illness.

As no psychotropic can be guaranteed as being safe during pregnancy, this question must be reframed so that it does not place the expectant mother's best interests in conflict with her baby's. A better question is, "Is it safest to take this medication, another medication, or no medication at all while pregnant (or breastfeeding)?" This more appropriate question, however, invites a series of additional questions.

What Risk Does This Illness Pose to the Mother and Her Child?

This question is not unique to mental illness. It is encountered whenever a pregnant or nursing mother has any illness that may necessitate pharmacotherapy. Understanding the risk associated with a mother's illness is the starting point in identifying the appropriate course of treatment. If an illness poses little risk to mother and child (e.g., allergic rhinitis), then only minimal pharmacological risk can be justified. However, medications carrying significant risk may be acceptable and even preferable if they provide protection from an illness that poses great risk to mother or child (e.g., epilepsy, HIV).

There are rapidly growing data regarding the deleterious impact of psychiatric illness during pregnancy and the postpartum period. It is now well established that moderate to severe depression and anxiety, as well as manic and psychotic syndromes, jeopardize the well-being of both mother and child, carrying short-term and long-term implications for child health and development. The same holds true for perinatal substance use disorders. However, the data are less clear for some psychiatric disorders. For example, there is no compelling evidence to indicate that maternal attention-deficit disorder, left untreated, puts mother or child at immediate risk; however, it may do so indirectly. Specifically, if suspending attention-deficit disorder treatment leaves a pregnant or postpartum patient feeling overwhelmed by her inability to cope with the demands of her day-to-day responsibilities, she may be more susceptible to worsening depression and anxiety, which would pose risk.

How Likely Is This Illness to Recur or Worsen Without Pharmacotherapy?

Ideally, an expectant mother would be able to remain well despite stopping psychotropic treatment, sparing mother and child the risks attributable to both illness and pharmacological exposure. It was once believed that pregnancy was a time of emotional well-being that conferred protection from mental illness; however, research in recent decades indicates this is not the case. Women with preexisting histories of mood, anxiety, or psychotic disorders who discontinue psychotropic treatment at conception are highly vulnerable to a recurrence of illness during pregnancy. Unfortunately, existing research has not yet made it possible to reliably identify, in advance, the small subset of women who will remain well during pregnancy after discontinuing psychiatric medication.

Clinicians may also consider the individual patient's prior course of psychiatric illness when trying to determine whether an interruption in psychotropic treatment is advisable. Pertinent questions include: How many previous episodes of illness has she experienced? How severe were the prior episodes? Were psychotic symptoms present? Has she previously had a period of sustained euthymia after stopping psychiatric medication? Did previous recurrences arise gradually or abruptly? With resumption of treatment, how quickly does the illness resolve? And finally, has she experienced a recurrence or worsening of her illness during or after a previous pregnancy?

Can This Illness Be Successfully Treated Without Medication?

Bipolar disorder and schizophrenia, by definition, require psychotropic pharmacotherapy for effective management. However, many other psychiatric illnesses (e.g., depression and anxiety disorders) can be managed effectively with evidence-based psychotherapy for some patients in the absence of psychotropic medication. Again, reviewing the patient's past psychiatric history, specifically her motivation for and past benefit derived from psychotherapy, can offer insight into the potential effectiveness of a psychotherapy-alone treatment plan. If the patient presents for a preconception evaluation having never previously received psychotherapy, she can be asked to

postpone conception long enough to engage in psychotherapy and then determine whether she can successfully discontinue psychotropic treatment. In any event, in light of its synergistic benefits, psychotherapy should be routinely recommended even to those for whom medication must be continued.

Complementary interventions of low risk, such as daily exercise, prenatal yoga, and meditation, although not "treatments" for mental disorders per se, may contribute to an overall sense of well-being and can be considered. However, naturopathic supplements (e.g., St. John's wort, *Rhodiola rosea*, saffron, lavender, maharishi amrit kalash, mentat) are not recommended during pregnancy because they are not subject to FDA scrutiny, and reproductive safety data are sparse. Pregnant and breastfeeding women should be reminded that just because a substance is produced in nature does not mean that it is safe to expose a fetus or breastfeeding infant to it.

Which Medication(s) Should Be Chosen?

Pregnancy and lactation are not times to experiment with novel treatments; thus, choosing the best medication from the outset is critical. The ideal medication balances safety and efficacy. All too often, understandably preoccupied with the safety profiles of available medications, clinicians lose sight of the need for an efficacious treatment, ill-advisedly switching to an ineffective medication simply because they understand it to be "safer." If the rationale for administering a medication during pregnancy (or breastfeeding) is to protect mother and child from an illness, then a medication is advisable only if there is a reasonable expectation of protective benefit.

For ethical reasons, clinical trials to determine psychotropic efficacy are rarely, if ever, conducted during pregnancy and breastfeeding. Only a handful of observational studies have explored this question. Thus, the best available means to determine the likely efficacy of a given medication for a particular patient is to review her treatment history. Even a medication with a favorable reproductive safety profile is difficult to justify if a previous adequate trial of it has failed for the patient. Obtaining a comprehensive treatment history documenting the efficacy, tolerability, dosage, and treatment duration for each agent is instrumental in narrowing the list of viable medication choices. Particularly important is the utility of a medication during or immediately after a previous pregnancy.

After medications with a reasonable likelihood of efficacy have been identified, safety considerations enter the decision-making process. It is important to review the reproductive safety profiles of agents deemed likely to provide therapeutic efficacy, taking into consideration the gestational timing when the decision is being made. The ideal medication regimen lies at the intersection of the efficacy and safety survey. If multiple agents remain under consideration, then the choice can be further refined in terms of potential tolerability during gestation. The scope of tolerability includes selecting agents that are less likely to contribute to pregnancy-related conditions such as gestational diabetes and gestational hypertension.

Is It Better to Reduce Medication Dosages When Pregnant or Breastfeeding?

Prescribing the minimal effective dosage is especially important during pregnancy and lactation. Upon learning that a patient is pregnant, clinicians and patients often instinctively

lower psychotropic dosages in an effort to reduce fetal exposure, but indiscriminate dosage reduction may increase the vulnerability to relapse. If the therapeutic objective is to eliminate the child's exposure to maternal illness while minimizing the child's psychotropic exposure, then perinatal dosage management must be informed by an understanding of the factors governing the alterations in drug disposition across gestation and through the placental passage and excretion into breast milk.

Dosage adjustments may be necessary to maintain a medication's efficacy during pregnancy. For example, it may be necessary to increase the dosage of TCAs to approximately 1.6 times the preconception dosage to maintain therapeutic concentrations in late pregnancy (Altshuler *et al.* 1996; Wisner *et al.* 1993). Small studies investigating SSRIs have demonstrated clearance changes across pregnancy and dosage adjustments in response to increasing maternal symptoms (Hostetter *et al.* 2000; Freeman *et al.* 2008; Sit *et al.* 2008). However, the pattern of dosage adjustment needed during gestation is not uniform for all medications. For example, among anticonvulsant and mood-stabilizing medications, serum concentrations of lamotrigine (Ohman *et al.* 2000; Pennell *et al.* 2004; Polepally *et al.* 2014; Tran *et al.* 2002) and valproate (Otani 1985; Philbert *et al.* 1985) decline steadily across gestation, whereas carbamazepine concentrations (Bardy *et* *al.* 1982b; Battino *et al.* 1982; Bologa *et al.* 1991; Dam *et al.* 1979; Lander *et al.* 1981; Omtzigt *et al.* 1993; Otani 1985; Tomson *et al.* 1994; Yerby *et al.* 1985) exhibit smaller changes that are primarily evident only in late pregnancy. These alterations in drug concentrations and dosing requirements are probably a consequence of the impact of the physiological changes of pregnancy on the pharmacokinetics (Boobis and Lewis 1983; Frederiksen 2001; Little 1999; Wyska and Jusko 2001) and possibly the pharmacodynamics (Wyska and Jusko 2001) of psychotropic medications. Ultimately, an improved understanding of the factors governing perinatal pharmacokinetic and pharmacodynamic alterations may enable the construction of personalized dosing strategies during gestation.

The level of fetal psychotropic exposure is another key consideration. All psychotropics studied to date cross the human placenta, yet there are significant differences in placental passage rates. Bidirectional placental transfer is mediated primarily by simple diffusion, and determinants of the transplacental diffusion rate include molecular weight, lipid solubility, degree of ionization, and protein-binding affinity (Audus 1999; Moore *et al.* 1966; Pacifici and Nottoli 1995). In addition, placental P-glycoprotein, which actively transports substrates from the fetal to the maternal circulation, is probably a key determinant of fetal psychotropic exposure. Consequently, medications with greater affinity for P-glycoprotein should be associated with lower fetal-to-maternal medication ratios, as has been demonstrated in an investigation of antipsychotic placental passage (Newport *et al.* 2007a). Furthermore, clarification of the factors governing placental passage may ultimately contribute to the development of psychotropic agents with minimal rates of placental transfer (Wang *et al.* 2007).

However, fetal plasma concentrations are not the ultimate measure of functional psychotropic exposure and may even underestimate the more critical measure of fetal brain concentration. Certain physiological attributes of the human fetus, including high cardiac output, increased blood-brain barrier permeability, low plasma protein concentrations and plasma protein binding affinity, and low hepatic enzyme activity (Bertossi *et al.* 1999; Morgan 1997; Oesterheld 1998), may produce higher fetal CNS concentrations of psychotropic medications than might be anticipated from circulating levels. Preclinical investigations by our group have demonstrated that transplacental passage results in high levels in fetal CNS tissues and significant binding at neurotransmitter receptor and transporter sites (Capello *et al.* 2011).

Similar considerations apply when endeavoring to minimize the psychotropic exposure of nursing infants. Because the neonate exhibits low hepatic enzyme activity (Warner 1986) and glomerular filtration and tubular secretion rates (Welch and Findlay 1981), psychotropic exposure may be higher than anticipated for breastfed infants. A model to predict rates of breast milk excretion from characteristics of the molecular structure of candidate medications has been proposed (Agatonovic-Kustrin *et al.* 2002). Such models may allow clinicians to estimate a nursing infant's exposure without subjecting the infant to invasive procedures.

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CHAPTER 64

Treatment of Attention-Deficit/Hyperactivity Disorder in Adults

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Definitions and Diagnostic Criteria

DSM-5-TR defines ADHD as "a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development" (American Psychiatric Association 2022, p. 68). Furthermore, the pattern of inattention and/or hyperactivity must be inappropriate for the age. DSM-5-TR also specifies the characteristics of distinctive behaviors that suggest inattention and/or hyperactivity-impulsivity; these behaviors are not merely symptoms of underlying oppositional behavior, hostility, inability to understand instructions, or defiance. DSM-5-TR diagnostic criteria for ADHD (see Box 17-1) also stipulate onset of symptoms prior to age 12, evidence that the condition interferes with daily functioning, hyperactive or inattentive symptoms manifesting in two or more distinct settings, and assurance that the symptoms are not secondary to a psychotic disorder or other mental illness.

Box 64-1. Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

   1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

      Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

      a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
      b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
      c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
      d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
      e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
      f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
      g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).

    h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
    i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

    a. Often fidgets with or taps hands or feet or squirms in seat.
    b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
    c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
    d. Often unable to play or engage in leisure activities quietly.
    e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
    f. Often talks excessively.
    g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
    h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
    i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

F90.2 Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

F90.0 Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

F90.1 Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

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Although diagnostic criteria for children, adolescents, and adults are the same, the number of criteria that must be met differs between youth and adults. For both attention symptoms and hyperactivity/impulsivity symptoms, at least five out of the nine criteria must be met to establish a diagnosis of ADHD in adults, and at least six of nine in individuals less than 17 years of age.

ADHD is a common psychiatric disorder; approximately 4% of adults are estimated to suffer from the disorder worldwide. The disorder was first acknowledged in the scientific literature in 1775 in a German textbook written by Melchior Adam Weikard. Despite ADHD's long history and prevalence, it has been strikingly unrecognized in adults. Experts believe that ADHD was underdiagnosed and unrecognized in adults until the 1990s, over 200 years after its establishment in the scientific literature. ADHD, one of the most pervasive psychiatric conditions among children, often fails to remit as these children enter adulthood. Agnew-Blais *et al.* (2016) reported that 21.1% of children diagnosed with ADHD in childhood continued to have symptoms that met criteria for that diagnosis at 18 years of age. Even some subclinical or subthreshold ADHD symptomatology can be problematic and interfere with social, educational, and occupational functioning. Brown and Casey (2016) found that college students with subclinical

ADHD symptoms also experienced problems with externalizing behaviors and executive functioning.

Although many young adults with ADHD may not have symptoms that meet the full diagnostic criteria after a childhood diagnosis, the vast majority retain at least some symptoms and/or functional impairment (Faraone *et al.* 2016). Faraone *et al.* (2006) took a closer look at the threshold of symptoms required for a diagnosis of ADHD. The study investigated whether degrees of functional impairment and psychiatric comorbidity in patients with subthreshold and late-onset ADHD were similar to those in patients with a formal diagnosis of ADHD. Researchers found that patients with late-onset ADHD experienced functional impairment and psychiatric comorbidity at rates similar to those among patients with "full" ADHD. Patients with subthreshold ADHD did not have impairment and comorbidity to the degree that those with full ADHD did, but in comparison with patients without ADHD, they were significantly more afflicted. Compared with patients without ADHD, patients with subthreshold ADHD had higher rates of academic and occupational difficulties. Oppositional defiant disorder was also more prevalent among patients with subthreshold ADHD (Faraone *et al.* 2006). Thapar and Cooper (2016) drew a similar conclusion: patients with subthreshold ADHD experienced poorer academic achievement compared with patients without ADHD. The investigators noted that there was no definite threshold of ADHD symptoms that guaranteed impairments.

Until recently, ADHD was not recognized as a clinical entity among adults. ADHD symptoms in adults have been particularly difficult to identify; they typically differ from those in children, in that the attention deficit is the primary concern, not the motoric hyperactivity. Whereas children with ADHD experience inattention and difficulty with focus and concentration, adults with ADHD may present with an inability to complete tasks at work or school. The hyperactivity that is a hallmark of childhood ADHD typically appears as restlessness in adults. Neither restlessness nor problems at work or school may be interpreted as pathological by clinicians, and may not be immediately recognized as signs and symptoms of adult ADHD. The lack of recognition of the clinical significance of adult ADHD has been problematic, considering that 3.2% of adult women and 5.4% of adult men have symptoms that meet diagnostic criteria (Faraone *et al.* 2006). Interestingly, the ratio of men to women with adult ADHD is about 1:1, in contrast to youth ADHD, in which the ratio of boys to girls is 4:1.

The age at onset of ADHD has recently been questioned by some investigators. Since ADHD is classified as a neurodevelopmental disorder, symptoms must be present before age 18; however, studies have shown that many adult ADHD patients deny or were not aware of symptoms in childhood. Thapar and Cooper (2016) examined the results of multiple studies on adult-onset versus childhood-onset ADHD. They concluded that adult-onset and childhood-onset ADHD were phenotypically similar conditions with different underlying neural mechanisms and causal influences.

Neurobiology: Genomics and Neuroimaging

Genomics

Research has established that genetic vulnerability plays a substantial role in the presentation and development of ADHD, with about 80% of the phenotypic differences accounted for by genetics. Zametkin and colleagues first reported in 1998 that differences in the dopamine transporter gene may be linked to the development of ADHD (Zametkin and Liotta 1998). More recently, another research team investigated the relationship between genes responsible for sphingolipid metabolism and ADHD (Henriquez-Henriquez *et al.* 2020). This study was groundbreaking, considering that prior research had shown that patients with ADHD may have differences in myelination compared with control subjects. The 2020 study concluded that ADHD was correlated with variations in eight of the genes responsible for sphingolipid metabolism. ADHD and ADHD-like symptoms are also often found in individuals with genetic syndromes such as Williams syndrome, 22q11 microdeletion, fragile X syndrome, and tuberous sclerosis and are manifestations of the underlying biological etiology (Henriquez-Henriquez *et al.* 2020).

Neuroimaging

In addition to genetics, numerous neurobiological factors have been established in the pathophysiology of ADHD. Neuroimaging has been an invaluable tool in understanding ADHD. In a groundbreaking review, Zametkin and Liotta (1998) concluded that there were various differences in both structural and functional brain imaging between individuals with ADHD and a control group. Patients with ADHD demonstrated differences in basal ganglia anatomy and glucose metabolism. Structural differences were also seen in the corpus callosum, caudate, and cerebral cortex. Decreased total cerebral volume was found in patients with ADHD compared with control subjects. The investigators reported that dopamine, serotonin, and norepinephrine were uniquely responsible for the behavior changes observed in individuals with ADHD, arguing that the interplay between norepinephrine and dopamine was especially critical. Zametkin and Liotta cited a prior study (Oades 1987) that reported that dopamine abnormalities were responsible for behavioral changes such as inattention, tics, self-mutilation, and hyperactivity. Additionally, the investigators cited a study (Mercugliano 1995) that concluded that dysfunction of the frontal striatum may play a role in the development of ADHD. These findings support the concept that dopamine and norepinephrine play a significant role in the symptomatology of ADHD (Zametkin and Liotta 1998).

Changes in morphological appearance of the cortex and catecholamine signaling have both been associated with the neurobiological mechanisms of ADHD. Cherkasova and colleagues, in 2017, sought to determine the relationship between cortical morphology and catecholamine signaling in patients with ADHD. These investigators found that ADHD patients were likely to have a thinner cortex in regions of the brain associated with the dopamine D_2 and D_3 receptors. Interestingly, the study identified a possible association between cortical thickness and dopamine transmission in patients who were treatment naive and had confirmed ADHD. This finding suggests that neurobiological changes in patients with ADHD may be independent from changes associated with treatment (Cherkasova *et al.* 2017).

Psychiatric Comorbidity

In children, a diagnosis of ADHD is frequently associated with comorbid psychiatric disorders such as tic disorders, learning disorders, intellectual developmental disorder

(intellectual disability), oppositional defiant disorder, conduct disorder, and autism spectrum disorder. As with youth, adults with ADHD have been reported to have a high prevalence of psychiatric comorbid disorders. Longitudinal studies have demonstrated that ADHD is associated with numerous psychiatric comorbidities and social impairments. In a study by Ramos Olazagasti *et al.* (2013), risky behavior in adults with ADHD was associated with increased medical comorbidity; however, only study participants with a dual diagnosis of antisocial personality disorder/conduct disorder and ADHD were found to have increased medical comorbidities. The study authors also found that early use of ADHD medications was protective against and not associated with increased medical comorbidities over time (Ramos Olazagasti *et al.* 2013). Similarly, Thapar and Cooper (2016) reported that although ADHD is not associated with increased medical comorbidity, there is an increased overall risk of mortality. According to their findings, the increased risk in mortality is linked to accidents and a dual diagnosis of antisocial personality disorder, substance use disorder, or oppositional defiant disorder (Thapar and Cooper 2016).

That same study also noted that patients with ADHD experienced more psychosocial problems compared with patients without ADHD (Thapar and Cooper 2016). ADHD was a strong predictor of drug misuse in adolescence and antisocial behaviors, leading to involvement with law enforcement. Interestingly, the meta-analysis found that 26% of incarcerated adults suffered from ADHD. Pharmacological treatment has been found to decrease the rate of criminal activity among ADHD patients, and the alarmingly high prevalence of ADHD among imprisoned adults highlights the necessity for earlier intervention (Thapar and Cooper 2016).

Adler *et al.* (2011) reported that older ADHD patients had impairments in three critical life domains: home, social, and work. Patients were found to be at a significantly higher risk of dropping out of high school compared with their counterparts without ADHD. Occupational problems in ADHD patients included being fired from a job or reprimanded at work, being tardy at work, being unemployed, and having multiple jobs. Compared with those without ADHD, individuals with ADHD were found to have poorer relationships with their parents. They also had higher rates of sexually transmitted infections and were twice as likely to divorce. Patients with ADHD were also less likely to have saved for retirement, but more likely to have been arrested or involved in a motor vehicle accident. Adler et al.'s study posited that treatment should focus not only on treatment of the psychiatric symptoms of ADHD but also on the psychosocial problems associated with the disorder. Adler *et al.* (2011) reported that in addition to pharmacotherapy, cognitive-behavioral therapy (CBT) could be beneficial for both the comorbid anxiety and depression and the psychosocial impairments from which patients may suffer.

Katzman *et al.* (2017) reported that commonly co-occurring disorders in adults with ADHD include anxiety, depression, substance use disorder, personality disorder, and bipolar disorder. The authors argued that the overlap among symptoms of ADHD, the comorbidities, and symptoms of each individual comorbid disorder was so robust that ADHD should be viewed as a spectrum of disorders instead of a single, categorical disease. The rate of comorbid psychiatric disorders among patients with ADHD is astoundingly high, and the Katzman team cited a prior study concluding that 65% of patients younger than 18 years had comorbid bipolar disorder (Tamam *et al.* 2008). Katzman and colleagues also reported that comorbid ADHD was present in 7.8% of patients with depression. The rate of anxiety disorders in individuals with ADHD was nearly 50%, while the rate of personality disorders was over 50%. Although the authors did not report a specific percentage of adult patients with ADHD with comorbid substance use disorders, they noted that patients with ADHD were found to use substances at a younger age compared with their counterparts without ADHD, experienced increased difficulty in achieving abstinence, and had higher rates of polysubstance abuse. Importantly, Katzman *et al.* (2017) reported that early treatment with stimulants may prevent psychiatric comorbidities later in life.

Long-Term Outcomes

ADHD has been associated with several significant negative functional outcomes. Klein *et al.* (2012) evaluated long-term outcomes of patients with ADHD. They found that participants diagnosed with ADHD had, on average, 2.5 fewer years of education and decreased occupational success compared with the control group. They also reported that the group with a diagnosis of ADHD had almost triple the rate of incarceration and death compared with the control group. Patients with ADHD also report higher rates of divorce and marital difficulties compared with control subjects (Klein *et al.* 2012).

Clinical Evaluation

Because there is no specific diagnostic test for ADHD in adults, a detailed, comprehensive history from the patient is essential. It is often helpful to obtain information from the spouse, because ADHD symptoms frequently impact family relationships. If available, childhood history from parents of adults can be helpful, including school records and report cards. A thorough medical workup, including physical examination and laboratory assessment, should be completed. Evaluation for obesity, thyroid disease, and sleep disorders should be performed. For example, hyperthyroidism could be the cause of hyperactivity, and hypothyroidism the cause of inattention. Sleep disorders, such as sleep apnea, which is compounded by obesity, could result in increased daytime sleepiness and inattention. Neurological disorders such as dementia, traumatic brain injury, vascular disease, and stroke should be ruled out. Additionally, hormonal changes in women should be considered in the differential. A comprehensive review of medications is critical for the medical workup of ADHD; anticholinergics, antihistamines, bronchodilators, anticonvulsants, muscle relaxants, and narcotics can be potential causes of ADHD-like symptoms.

In adults who are candidates for medication, particular attention to cardiovascular status should be paid. A detailed cardiovascular history should be taken, and a baseline electrocardiogram is recommended. In individuals with a history of cardiovascular disease, additional consultation with a cardiologist and an echocardiogram may be helpful. Standardized rating instruments, such as the Conners Adult ADHD Rating Scale, Adult ADHD Clinical Diagnostic Scale, Adult ADHD Self-Report Scale, Brown Attention-Deficit Disorder Symptom Assessment Scale, Barkley Adult ADHD Rating Scale, Wender Utah Rating Scale, Clinical Global Impression (CGI) scale, and

Patient Global Impression--Improvement scale, can be useful in the evaluation of symptom severity. Neuropsychological testing may be indicated to differentiate underlying learning disorders and/or executive functions problems, which frequently co-occur, from ADHD.

Specific neuropsychological assessment of executive functions should be included, because problems in this area frequently co-occur with ADHD. Frequently used neuropsychological assessment tools include the Wechsler Adult Intelligence Scale--Revised (WAIS-R) Similarities test, Wisconsin Card Sorting Test, Controlled Oral Word Association Test, WAIS-R Block Design test, Rey-Osterrieth Complex Figure Test, Embedded Figures Test, California Verbal Learning Test, Wechsler Memory Scale, Trail Making Test, WAIS-R Digit Symbol test, Continuous Performance Test, and the 3RT Test Simple task. These tests assess a variety of functional domains often implicated in ADHD-related problems, such as verbal intelligence, fluency, executive functions, visual-figural problem-solving, abstract problem-solving, working memory, simple attention, sustained attention, focused attention, verbal memory, and figural memory.

Overview of Treatment

The goal of treatment of ADHD in adults is to reduce symptoms, alleviate distress and impairment, and improve quality of life. Because adult ADHD symptoms are likely to impact family members, it may be helpful to include the spouse in treatment planning. Successful treatment response is measured by reduction in clinical symptoms and functional impairment. Although there are no specifically recommended quantitative measures of treatment response in adults, most practitioners aim for a 30% reduction in ADHD symptoms. CGI-Improvement scores for ADHD symptoms may be helpful to monitor response.

Pharmacological Treatments

Investigation of pharmacological treatment of adult ADHD has only rather recently been established. Studies examining safety and effectiveness of adult ADHD treatments have lagged behind those of children and adolescents. As with youth, stimulants are generally recommended as first-line pharmacotherapy for adults with ADHD. Although controlled studies in children and adolescents typically report a response rate of 70%, response rates in controlled trials of adults are more variable, ranging from 25% to 78% (Wilens *et al.* 2011). Wilens and colleagues reported a short-term controlled weighted mean response rate of 60% and a longer-term weighted mean of 74%. As in youth, efficacy rates for amphetamines and methylphenidate are similar in adults. Variable adult response rates may be a function of differences in diagnostic criteria, dose range, impact of psychiatric comorbidity, and lack of consistent response measures.

Unlike in children and adolescents, there are very few studies evaluating the efficacy of individual pharmacological treatments of ADHD in adults. To date, there are no head-to-head studies available.

Simon *et al.* (2015) reported that stimulants are currently the first-line medication choice for treatment of ADHD symptoms, given their mechanistic ability to block norepinephrine and dopamine transporters, resulting in increased dopamine in the

extracellular space. The authors recommend a sustained-release version of stimulant medications, which is typical of current practice (Simon *et al.* 2015). Important aspects of each medication are outlined in Table 64-1. Efficacy parameters of FDA-approved pharmacological treatments are summarized in Table 64-2.

TABLE 64-1. Pharmacological treatment of ADHD in adults

Treatment	**Mechanism of action**	**Recommended dosage range**	**FDA approved for treatment of ADHD in adults**	**Strength of evidence**
Dextroamphetamine-amphetamine	Blocks dopamine, norepinephrine, and serotonin reuptake, and increases release from the presynaptic terminal	5-40 mg/day	Yes	Strong
Lisdexamfetamine	Blocks dopamine, norepinephrine, and serotonin reuptake, and increases release from the presynaptic terminal	10-70 mg/day	Yes	Strong
Methylphenidate	Inhibits reuptake of dopamine and norepinephrine and	5-60 mg/day	Yes	Strong

Treatment	Mechanism of action	Recommended dosage range	FDA approved for treatment of ADHD in adults	Strength of evidence
	promotes dopamine release			
Atomoxetine	Selectively inhibits norepinephrine reuptake	40-80 mg/day	Yes	Strong
Guanfacine (extended release)	Inhibits norepinephrine release and activates a_{2a}-adrenergic receptors	1-4 mg/day	No	Moderate
Clonidine	Activates a_{2a}-adrenergic receptors	0.1-0.4 mg twice a day	No	Moderate
Bupropion	Unknown	200 mg, up to 450 mg	No	Moderate

TABLE 64-2. Efficacy of FDA-approved pharmacological treatments

Treatment	Efficacy
Amphetamine	Weighted mean approximately 61% response vs. 20% placebo

Treatment	Efficacy
	Decrease in ADHD symptom scores on Clinical Global Impression scale of 33%
Lisdexamfetamine	Statistically significant improvement in ADHD symptoms vs. placebo
	Remission of symptoms achieved in 64%-72.1% of study participants
Methylphenidate	Weighted mean approximately 60% response vs. 26% placebo
	Number needed to treat (NNT) = 1.1
Atomoxetine	Statistically significant improvement in ADHD symptoms vs. placebo
	NNT = 4

Stimulants

There are two classes of CNS stimulants for treatment of ADHD in youth and adults, which include amphetamines and methylphenidate. Because of their abuse potential, both medication classes are designated Schedule II controlled substances as classified by the FDA. It is important to note that stimulants should not be used to treat hyperactivity or impulsivity in individuals whose symptoms are secondary to a comorbid psychiatric illness or environmental factors.

Dextroamphetamine-Amphetamine

The amphetamines are CNS stimulants that reduce hyperactivity and impulsivity and other ADHD symptoms. Amphetamine blocks the reuptake of dopamine and norepinephrine in the presynaptic cleft and promotes intracellular release. The peak plasma concentration of amphetamine is reached approximately 3 hours after administration. The half-life of the medication follows pharmacokinetics that are proportional to the dose.

Amphetamine was first discovered in 1937 by Charles Bradley. At that time, he tested the efficacy of Benzedrine, an original amphetamine enantiomer, in 30 school-age children. He found that there was a significant increase in school performance among study participants that was entirely attributable to the use of the drug.

Amphetamine is FDA approved for the treatment of narcolepsy and ADHD. Mixed amphetamine salts, currently the most commonly prescribed amphetamine for youth, are a mixed enantiomer version of amphetamine. In general, the amphetamines are relatively well tolerated in youth and most adults. The more common adverse effects that have been reported in association with use of amphetamine are cardiovascular events, hypertension, worsening and induction of psychosis, precipitation of a mixed/manic episode in patients with preexisting bipolar disorder, tics, visual disturbances, seizures, and aggression. In children, stimulants may be associated with suppression of long-term growth (Heal *et al.* 2013).

Lisdexamfetamine

Lisdexamfetamine is FDA approved for treatment of ADHD in children older than 6 years, adolescents, and adults. It is an amphetamine prodrug with a metabolic route distinct from that of the other amphetamines, in that it is broken down by red blood cells to create D-amphetamine and L-lysine. Lisdexamfetamine is a long-acting formulation, and thus there is less abuse potential (Heal *et al.* 2013).

Methylphenidate

Methylphenidate is a CNS stimulant with a mechanism of action distinct from that of amphetamine. It was first discovered in 1944 by the Ciba-Geigy Pharmaceutical Company. Now known as Novartis, the formulation was patented by Ciba-Geigy in 1954 under the trade name Ritalin. Methylphenidate is FDA approved for the treatment of ADHD in patients older than 6 years.

Methylphenidate is believed to both inhibit the reuptake of dopamine and norepinephrine and promote their release. Although the full mechanism of action is still unknown, methylphenidate has been proven to decrease hyperactivity and impulsivity. It has a half-life ranging from 2 to 7 hours and reaches its peak concentration 1-2 hours after administration.

The most commonly reported adverse effects of methylphenidate are appetite suppression and initial insomnia. Nervousness and tachycardia are also not uncommon. The insomnia caused by methylphenidate use can typically be alleviated by dosing in the morning instead of in the afternoon or evening. Cardiovascular effects are more likely in adults than in youth, and a medical workup is recommended prior to initiation (Heal *et al.* 2013).

Long-Acting Formulations

Long-acting formulations of stimulant medications are increasingly used in clinical practice for practical reasons. Both with youth and adults, once-a-day administration makes it more feasible to treat symptoms during the course of the schoolday or workday. Long-acting formulations are also often prescribed for individuals with ADHD and comorbid substance abuse because of their decreased abuse potential compared with short-acting formulations.

Pharmacological treatment of ADHD has been associated with improved long-term outcomes. Roy *et al.* (2018) took a closer look at predictors in childhood that had an impact on long-term functional outcomes of patients enrolled in the Multimodal Treatment of Attention Deficit Hyperactivity Disorder study (MTA). The authors concluded that early diagnosis and intervention in children with ADHD led to better functional outcomes as adults. Recognition and treatment of ADHD symptomatology were uniquely beneficial (Roy *et al.* 2018). Shaw *et al.* (2012), in a systematic review in 2012, came to similar conclusions. The review examined 30 years of studies on the impact of ADHD treatments on long-term outcomes. The authors reported that treatment reduces the negative impact ADHD can have on overall functioning. Untreated patients were found to have more severe impairments in functioning. Interestingly, patients treated for ADHD were not found to be at a higher risk of substance abuse compared with untreated patients. Of note, untreated

ADHD patients were more likely to experiment with cocaine compared with treated patients. Additionally, treatment for ADHD was found to decrease antisocial behaviors, drug use, and addictive behaviors. Treatment improved occupational and academic outcomes of patients as well. Research has also shown that pharmacological treatment of ADHD is associated with a decreased incidence of trauma-associated hospital visits and criminal activity (Shaw *et al.* 2012).

Unfortunately, long-term treatment with stimulants has been correlated with lower adult height. Greenhill *et al.* (2020) reviewed long-term outcomes of the original participants in the MTA and concluded that compared with the minimally medicated group, patients with 16 or more years of consistent stimulant use had slightly lower height on average in adulthood (Greenhill *et al.* 2020).

Nonstimulant Medications

Nonstimulant medications, including atomoxetine, a_2 agonists, bupropion, and tricyclic antidepressants, offer patients additional options for ADHD symptom relief. They are recommended for stimulant nonresponders and for adults with ADHD and significant comorbidity. Stimulant-naive patients may respond more robustly to atomoxetine when it is used before stimulants. Although the majority of children and adolescents benefit from treatment with a stimulant, there are fewer data regarding therapeutic adult response. Adults with ADHD tend to have more psychiatric comorbidity, including substance use disorders, which are common. It is estimated that 15%-20% of adults with a diagnosed substance use disorder carry a dual diagnosis of ADHD. Nonstimulant medications offer additional treatment options for individuals considered at high risk for medication misuse.

Although patients with ADHD are at a higher risk of substance abuse over their lifetimes, treatment of ADHD has been associated with a decreased risk of substance abuse. Quinn *et al.* (2017) reviewed 2,993,887 health care claims of children and adolescents over a 9-year period. The study evaluated the relationship between substance abuse and ADHD treatment and found that stimulant treatment of ADHD was not associated with an increased risk of substance abuse. Interestingly, treatment of ADHD was found to be protective against substance abuse. The study noted its similarity to a Swedish study (Chang *et al.* 2014) that also found a decreased incidence of substance abuse among patients treated with stimulants for ADHD. The Swedish study similarly concluded that stimulants were protective against future substance abuse (Quinn *et al.* 2017).

Guanfacine and clonidine have not been FDA approved for the treatment of ADHD in adults; however, they are included in this chapter because of the extant research on their effectiveness as off-label treatments.

Atomoxetine

Atomoxetine was the first medication to be approved by the FDA for treatment of ADHD in adults. It is unique among the nonstimulant medications in that it is a selective norepinephrine reuptake inhibitor. Originally intended for use as an antidepressant, atomoxetine was reported to decrease ADHD symptoms in trial participants. This medication is FDA approved for treatment of ADHD in children, adolescents, and adults. It is given in dosages ranging from 40 mg/day to 80 mg/day. It may be useful in adults with ADHD who have co-occurring substance use, anxiety, or tic symptoms.

Adverse effects may include nausea, weight changes, insomnia, constipation, dizziness, and sexual dysfunction. Atomoxetine has been assigned a black box warning for increased risk of suicidal ideation in children, adolescents, and young adults, but there have been no reports of suicidality in adults with ADHD. Individuals at risk for bipolar disorder should be closely monitored, because atomoxetine may increase risk of bipolar symptoms (Huang *et al.* 2020).

Guanfacine

Guanfacine is an a-adrenergic agonist effective in treatment of ADHD symptoms. In addition to its a-adrenergic effects, guanfacine inhibits the release of norepinephrine. It normalizes the balance between dopamine and norepinephrine in the amygdala through alteration of hyperpolarization-activated cyclic nucleotide-gated potassium channels. Guanfacine is available in short-acting and long-acting formulations. The long-acting formulation of guanfacine is the only one of the two that is FDA approved for treatment of ADHD; however, it is FDA approved for treatment of ADHD only in youth. It can be used both as a monotherapy and as an adjunct to other ADHD medications. It is given once daily, and the recommended dosage ranges from 1 mg/day to 4 mg/day. As the a-agonists have cardiovascular effects, blood pressure and heart rate should be monitored in patients taking guanfacine for ADHD (Iwanami *et al.* 2020a, 2020b).

Clonidine

Similar to guanfacine, clonidine hydrochloride is an a-adrenergic agonist that is effective in treating ADHD symptoms. It is available in a short-acting formulation and in an extended-release formulation. Like guanfacine, it has not been FDA approved for the treatment of adults with ADHD or in children younger than 6 years, but it can be used off-label. The recommended dosage ranges from 0.1 mg/day to 0.4 mg/day, typically given in twice-a-day dosing (Mattes 2016).

Bupropion

Bupropion is an antidepressant with mixed catecholamine effects that is FDA approved for treatment of major depressive disorder and seasonal affective disorder. It is used off-label for treatment of ADHD. Bupropion is offered in a sustained-release and an extended-release formulation. For the treatment of ADHD, the sustained-release formulation is given at dosages up to 200 mg/day; clinical effects last about 12 hours. The extended-release formulation is given at dosages up to 450/day, and the clinical effects last about 24 hours (Huang *et al.* 2020).

Tricyclic Antidepressants

Despite substantial use in youth, there are only two studies of tricyclic antidepressants in adult ADHD. A controlled study of desipramine at dosages up to 200 mg/day resulted in reduction of symptoms in as little as 2 weeks' time (Wilens *et al.* 2011).

Treatment of Adult ADHD With Comorbid Psychiatric Disorders

ADHD often co-occurs with other psychiatric disorders. The recommended treatment approach in adults with ADHD and psychiatric comorbidity is to treat the disorder causing the most distress and/or impairment first. In cases of mild depression, CBT can be helpful for both the depression and the ADHD. Stimulants have successfully been given in combination with antidepressants in patients with more impairing depressive disorders. Bupropion could be considered a first-line treatment of patients with ADHD and comorbid major depressive disorder as monotherapy; a selective serotonin reuptake

inhibitor antidepressant and a long-acting stimulant could also be beneficial. Tricyclic antidepressants, such as desipramine and nortriptyline, and selective serotonin-norepinephrine reuptake inhibitors, such as venlafaxine, have also been used as monotherapy. Other options include antidepressants used in combination with a short-acting stimulant, atomoxetine, or lisdexamfetamine. In patients with bipolar disorder in which a stimulant could precipitate a manic episode, bupropion or other nonstimulant medications should be considered after the mania has resolved. Interestingly, stimulants have not been found to increase anxiety symptoms in patients with ADHD and comorbid anxiety disorders. For patients with substance use disorders, most experts recommend treatment of the substance use disorder first, followed by treatment of the ADHD once the substance use disorder has remitted. Treatment of ADHD symptoms has been found not only to reduce the severity of comorbid substance abuse, depression, anxiety, and bipolar disorder but also to be protective against future psychiatric illness.

Psychosocial Treatment Options

Nonpharmacological treatment options for ADHD include CBT, dialectical behavior therapy, and mindfulness. Studies on the efficacy of nonpharmacological treatments for ADHD have reported benefit in children and adolescents. CBT is considered a mainstay in the treatment of ADHD; however, despite the availability and increasing popularity of CBT, dialectical behavior therapy, and mindfulness, research has shown a clear benefit of pharmacological treatments over nonpharmacological treatments.

Coaching and assistance with executive functioning have been found to be uniquely helpful in ADHD patients. Coaching is a relatively new treatment modality in ADHD; the intervention involves a patient working with a coach one-to-one or in a group setting. Coaching has been found to help patients meet individual treatment goals; the coach teaches patients how to maintain focus, build motivation, and overcome impairments. A major aspect of coaching is helping patients gain insight into their condition and recognize their impairments (CHADD 2021).

Although pharmacological treatments have been found to be superior, psychosocial treatments can be useful adjuncts for ADHD. A 2019 study of adult ADHD compared CBT treatment alone and CBT treatment in combination with a psychotropic medication. The study concluded that CBT is efficacious in treating adult ADHD; however, the combination of CBT and pharmacotherapy in adults with ADHD also improved executive functioning (Pan *et al.* 2019).

Combination Treatments

Research has shown that a combination of pharmacotherapy and psychosocial treatment is more beneficial than either treatment alone. Psychosocial treatments should be unique to each patient, addressing specific symptoms that are problematic. Ramos Olazagasti *et al.* (2013) recommended that adults with ADHD undergo psychosocial treatment for academic difficulties, tardiness, and maintenance of relationships, as well as other problems. CBT is a mainstay in the treatment of adult ADHD and focuses on giving patients tools to control impulsive behavior (Ramos Olazagasti *et al.* 2013).

In addition to the combination of pharmacotherapy and psychotherapy treatment, multiple ADHD medications have been used, off-label, in combination in patients who did not show an adequate response to monotherapy. Treuer *et al.* (2013) reported that the combination of atomoxetine and a stimulant was beneficial in some patients whose symptoms were not adequately controlled on one medication alone. The study did not find any additional safety concerns when using the medications in combination.

Recommendations and Clinical Applications

ADHD symptoms often persist into adulthood and carry concomitant risks of significant psychiatric comorbidity, functional impairment, and reduced quality of life. Comprehensive medical and psychiatric evaluation is indicated in adults to confirm an ADHD diagnosis and rule out other medical or psychiatric disorders, which frequently co-occur. Neuropsychological assessment of potential associated executive function problems is often necessary. Once a diagnosis has been confirmed, psychoeducation regarding ADHD outcomes and treatment is necessary. Adults with ADHD can be treated with the full range of pharmacological and psychosocial treatments available to youth. Because psychiatric comorbidity is the rule rather than the exception in adult ADHD, combination treatments are often necessary.

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CHAPTER 65

Treatment of Individuals With Intellectual Developmental Disorder

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In this chapter we focus on the pharmacological management of individuals with intellectual disability (ID) or intellectual developmental disorder (IDD). We will primarily use the term *IDD* here, although in practice the terms are used interchangeably. ID and IDD are a positive transition from the older classification, *mental retardation*, used in prior DSM editions. Care of individuals with IDD necessarily involves a comprehensive interventional approach that encompasses multiple systems of care and typically spans many decades of development, as reflected in the name of the condition. Therefore, use of psychotropic medications in this population is only one facet of the treatment plan, albeit an important one. Space limitations preclude an exhaustive overview of the myriad issues involved in providing care for this underserved population, so here we focus on treatment guidelines, with an emphasis on controlled studies in the IDD literature; additional resources are available that are wholly dedicated to IDD diagnosis and management, such as the Diagnostic Manual--

Intellectual Disability 2 (DM-ID-2; Fletcher *et al.* 2017). This chapter is intended to assist the general psychiatrist in making informed treatment decisions about pharmacotherapy, as well as in managing unique issues that arise in psychiatric treatment of individuals with IDD.

Background

IDD is a common condition, with estimates of total prevalence ranging from 0.7% to 1.35% (Boyle *et al.* 2011; Zablotsky *et al.* 2017). Presentation of IDD varies widely with regard to symptom severity, which is highlighted by increased emphasis on adaptive functional impairment in DSM-5 (American Psychiatric Association 2013). Indeed, diagnosis of IDD has gradually moved away from reliance on cognitive measurement of intellectual ability and increasingly toward operationalization of the impact of intellectual deficits on adaptive functioning. Unsurprisingly, mild IDD is more frequently identified in the broader population, whereas the prevalence of severe IDD (defined by approximate IQ < 35-40) is estimated at 2.5-6/1,000 children (American Psychiatric Association 2013; Committee to Evaluate the Supplemental Security Income Disability Program for Children with Mental Disorders *et al.* 2015).

DSM-5 specifies that for a diagnosis of an IDD, the individual must demonstrate deficits in intellectual functions, which may include deficits in reasoning, problem-solving, planning, abstract thinking, judgment, academic learning, and learning from experience. The presence of these impairments is confirmed through a clinical assessment involving IQ testing (e.g., Wechsler Intelligence Scale for Children, Wechsler Adult Intelligence Scale, Stanford-Binet Intelligence Scales) with results greater than two standard deviations below the mean (i.e., 70). The individual must also demonstrate deficits in adaptive functioning, and in fact, DSM-5 emphasizes this component more than previous editions. Such limitations prevent the individual from meeting developmental and sociocultural standards for independence and responsibility and involve limitations in one or more adaptive living skills, such as communication, independent living, and personal hygiene. Adaptive functioning reflects everyday functioning in the real world and includes practical activities of daily living, as well as social functioning and communication. Adaptive functioning is typically assessed via the Vineland Adaptive Behavior Scales, on which individuals with IDD score in the low range of functioning. Finally, the onset of disability must be during the developmental period (e.g., childhood), and thus an adult with new-onset cognitive limitations (e.g., traumatic brain injury, dementia) would not meet criteria for IDD.

There are multiple levels of severity, from mild to profound symptom burden (Table 65-1), and understanding the patient's level of IDD informs providers' ability to formulate an appropriate treatment plan. Approximately 78% of individuals with IDD have *mild* IDD, with a full-scale IQ of approximately 55-70 (Patrick *et al.* 2021), representing academic skills up to about the sixth-grade level. An individual with mild IDD will have some skills for independent functioning but will need support under stress. Individuals with *moderate* IDD represent approximately 12% of the IDD population (full-scale IQ: 35-40 to 50-55 [Patrick *et al.* 2021]). Their adjusted developmental age is approximately 6-9 years, and their presentation may be deceptive because of their varying cognitive profiles. For instance, language may range from actual conversations to the limited communication of basic needs (ranging from phrase speech to sentences). Individuals with strong language skills may confuse others into thinking that they understand and can manage more than they can. Individuals with *severe* to *profound* IDD represent about 1% of individuals with IDD and are typically identified very early in development through manifestation of motor and early language deficits. Individuals will have limited speech (e.g., single words or nonverbal) but may have stronger receptive language skills. Adults with severe IDD need lifelong assistance and highly supervised settings (e.g., group residences). They frequently have autistic features but may still form strong attachments to caregivers (Harris 2006). It is worth underscoring that IDD and autism spectrum disorder (ASD) are frequently comorbid, with approximately one-third (35%) of children with ASD also carrying a diagnosis of IDD (Maenner *et al.* 2021). Pharmacological management of ASD is discussed in Chapter 66, "Treatment of Autism Spectrum Disorder."

TABLE 65-1. Severity levels in intellectual developmental disorder

Severity level	**IQ**	**Adjusted developmental level**	**Language**	**Skills**
Mild	50-55 to 70	Ages 9-12 years	Simple sentences and conversations	Skills for some self-support; needs assistance under stress
Moderate	35-40 to 50-55	Ages 6-9 years	Sentences to phrases, varies	Needs sheltered conditions; can reach ~ 2nd grade academic level
Severe	20-25 to 35-40	Ages 3-6 years	Single words, limited spoken language	Minimal self-care, poor motor and language development; needs full supervision
Profound	20-25	Age < 3 years	Spoken language: very limited to none	Needs constant assistance and supervision

Source. Harris 2006.

Neurodevelopmental Framework

Given the typically early age at diagnosis of developmental disabilities and the age criterion in DSM-5, psychiatrists specializing in child and adolescent treatment are often the first to provide care. Notably, time dedicated to mastery of IDD is limited in child fellowship training, averaging as few as 3 hours of didactic instruction and one to five outpatient cases yearly (Marrus *et al.* 2014). This training gap is compounded by additional challenges that may manifest in IDD, depending on the severity of symptoms that result in asynchronous progression of chronological and developmental age. Challenges in assessing individuals with IDD include difficulties in obtaining subjective or objective symptom reporting, differentiating between manifestations of IDD and other comorbid psychiatric conditions, implementing treatment strategies effectively relative to neurotypical development, and overcoming logistical obstacles associated with complex health care delivery systems, particularly for individuals with severe IDD. A notable drop-off in services available for adults with IDD occurs as they age out of more comprehensive school and disability service systems, further complicating appropriate diagnosis and pharmacological management in this vulnerable population. Attention to systems of care around individuals with IDD is critical to their care and has important implications for their psychopharmacological treatment. Above all, medications should not be prescribed as the only intervention without other services and treatment provisions in place.

Assessment and Psychopharmacological Treatment Planning

Accurate assessment of psychiatric diagnoses for the purpose of psychopharmacological management is of particular importance in IDD. This assessment requires some adaptation of DSM criteria, especially for individuals with limited language. Assessment during the maintenance phases of pharmacological treatment requires the clinician to observe patients closely for any side effects from psychotropic medication--including extrapyramidal side effects (EPS), tardive dyskinesia, and sedation--that may not always manifest during subjective reporting. Collateral history from caregivers, school, and day programs is likewise of key importance, and descriptions of behaviors in specific contexts or environments, with rigorous behavioral analysis, are often needed to accurately identify the most important symptoms for treatment. It is beyond the scope of this chapter to detail the nuances of differential diagnosis in individuals with IDD, a topic that is comprehensively covered elsewhere (Fletcher *et al.* 2017).

In short, clinicians should maintain alertness for "diagnostic overshadowing"--defined as the misattribution of varying types of symptoms (whether medical, psychiatric, or part of the developmental disability) to an incorrect underlying cause--when assessing individuals with IDD. Examples include mistaking a component of IDD for a psychiatric symptom (e.g., repetitive behaviors in autism are mistaken for OCD) or, conversely, mistaking a component of psychiatric symptoms for a feature of IDD (e.g., a quiet patient is actually depressed, not simply nonverbal) (Jopp and Keys 2001). This error may be responsible for inaccurate diagnoses of bipolar disorder and schizophrenia in the IDD population (Charlot *et al.* 2007). Diagnostic overshadowing often occurs in the context of aggressive behaviors, a common presenting psychiatric problem in individuals with IDD that may be a manifestation of other underlying etiologies, such as medical problems (e.g., pain, infection, gastrointestinal disturbance), limitations in communication, psychosocial changes, trauma, anxiety, or depression. This is particularly relevant, given evidence that nonpsychiatric etiologies that may lead to disruptive behaviors in IDD are often underdiagnosed and undertreated (Axmon *et al.* 2016). To address similar clinical challenges in ASD, McGuire *et al.* (2016) developed clinical pathways for assessing irritability and problem behaviors in ASD, and this approach is also highly applicable to pharmacological assessment in individuals with other developmental disorders and intellectual disabilities. The focus of these clinical pathways is to assess for any contributors to aggression or other problem behaviors, such as medical comorbidities, communication difficulties, psychosocial stressors, negative reinforcement cycles, or co-occurring psychiatric disorders. This pathway approach provides a foundational model for approaching pharmacological management in IDD as well.

Psychopharmacological Treatment in Individuals With IDD

Unfortunately, literature on pharmacological management of IDD is limited. Most medication trials specifically exclude individuals with IDD, and so the evidence base is lacking in both child and adult psychopharmacology studies. Of the few clinical trials specific to IDD reviewed in this chapter, a number are underpowered, rely on nonspecific symptom outcomes (e.g., aggressive behaviors) rather than DSM-5 conditions, and have not been replicated. In the face of limited empirical research in this area, expert clinical consensus guidelines have recently been developed to provide a treatment framework in IDD (National Center for START Services 2023).

In clinical practice, medication strategies often draw on findings from randomized controlled trials (RCTs) in non-IDD populations, based largely on the premise that unless medication effects are influenced by co-occurring medical and neurological disorders, there is limited evidence that IDD itself changes the mechanism of action of psychotropic medications. Thus, while treatment of these conditions often aligns with treatment strategies used in individuals without IDD, particular caution should be taken when prescribing medications that cause or worsen cognitive impairment and sedation (e.g., chlorpromazine, topiramate, diphenhydramine) to individuals whose baseline cognitive functioning is limited. Additionally, individuals with IDD may be both more sensitive to medication side effects and less able to communicate about them.

Challenges in identifying specific pharmacological targets in IDD are due partly to substantial heterogeneity in etiological pathways converging on the IDD phenotype, which encompasses a range of genetic syndromes, prenatal exposures (e.g., alcohol), perinatal factors (e.g., prematurity, hypoxia), and environmental insults. Neurobiological systems affecting cognition are similarly diverse and wide-ranging, encompassing most classic neurotransmitter pathways (Zarrindast 2006). Relatedly, genetic and neurobiological findings implicate neuronal migration, synapse formation and plasticity, and cell signaling pathways, among others (Srivastava and Schwartz 2014; Vissers *et al.* 2016), underscoring the challenges in mapping these mechanistic pathways to tailored psychopharmacological interventions. This heterogeneity probably underlies the absence of disease-modifying treatments for core symptoms of IDD. However, the majority of adults (50%-70%) with IDD take some form of psychotropic medication (Axmon *et al.* 2017; Lunsky and Modi 2018; Tsiouris *et al.* 2013) for comorbid conditions.

Comorbidity in Individuals With IDD

Comorbidity is highly prevalent in the IDD population. Estimates indicate that 30%-50% of children and adolescents with IDD have a concurrent psychiatric diagnosis, compared with 8%-18% of youths without IDD (Einfeld *et al.* 2011). Estimates of psychiatric comorbidity in adults with IDD are similarly wide ranging, with studies reporting that 13%-75% of these individuals have co-occurring psychiatric symptoms (Buckles *et al.* 2013).

Commonly presenting symptoms for pharmacological treatment in this population include irritability; challenging or "problem" behaviors; aggression toward self, others, or objects; hyperactivity; agitation; stereotypies; and perceived oppositional behavior. Notably, anxiety, depression, and PTSD are infrequently discussed in IDD literature and may represent large domains of missed diagnoses in clinical practice. In a recent meta-analysis ($N = 6{,}151$), the most common symptoms for which children and adolescents with IDD presented to psychiatry were those indicating ADHD (30%) and anxiety disorders (7%-34%) (Buckley *et al.* 2020).

Similarly, rates of trauma and abuse were found to be substantially higher in individuals with developmental disabilities than in the general population (Constantino *et al.* 2020), yet they are underdiagnosed and undertreated. Relatedly, relatively benign treatments (e.g., selective serotonin reuptake inhibitors [SSRIs], behavioral therapy) may be overlooked in favor of medications with less favorable side-effect profiles, such as antipsychotics and mood stabilizers.

Psychopharmacological Approaches and Interventions

For reasons outlined above, a clearly determined DSM-5 diagnosis as a treatment target provides reliable guidance for ongoing complex pharmacological management. Medication management for a symptom, such as unspecified aggression, rather than a psychiatric condition, is best limited to situations in which individuals pose a risk of serious injury to self or others or are at risk of losing access to an important service (e.g., needing to move out of their home or change schools), or in which other treatments have failed to improve symptoms despite adequate psychosocial support. Care should be taken to avoid prescribing psychotropic medications for the convenience of the caregiver or as a substitute for a positive behavioral support plan and appropriate wraparound services. In patients with medical comorbidities, opportunities for simplification and consolidation of medication regimens should also be considered (e.g., choosing an anticonvulsant drug with desired psychopharmacotherapeutic effects with comorbid epilepsy). As-needed medication for behavioral symptoms has potential for overuse, necessitating clear and specific indications for use, frequent monitoring, and clear parameters for duration of treatment. Also, a significant concern with prior studies is failure to examine pharmacological effects in conjunction with evidence-based behavioral therapies, which are typically mentioned only insofar as they were included in the research design. There continues to be a lack of robust direct comparison of pharmacological and nonpharmacological treatments, separately or in combination, to guide clinical parameters for multidimensional treatment plans.

Psychopharmacological Management of Irritability and Aggressive Behaviors

Earlier psychopharmacology studies largely reported nonspecific symptom outcomes, including aggression, irritability, self-injurious behaviors (SIBs), and agitation. This tendency reflects clinical practice, where nonspecific irritability and aggressive behaviors are often the leading reasons for referral for psychiatric care. As

discussed previously, these symptoms are often a final common behavioral pathway with multiple possible etiologies, necessitating a thorough behavioral evaluation. When medication is indicated, first-generation and atypical antipsychotics are often used, despite minimal evidence for the benefits of chronic administration (Deb and Unwin 2007; Deb *et al.* 2015; Tyrer *et al.* 2008). Nevertheless, it is estimated that 20%-70% of individuals with IDD who exhibit aggressive or "problem" behaviors receive long-term pharmacological treatment (Axmon *et al.* 2017; Deb and Unwin 2007; de Kuijper *et al.* 2010; Gomes *et al.* 2019; O'Dwyer *et al.* 2016). When appropriate, however, medications judiciously used across shorter durations may be of benefit for symptom reduction.

Antipsychotics

The most robust data for youths with IDD have shown risperidone to improve symptoms of irritability and aggression and problem behaviors associated with disruptive behavior disorders (DBDs) (Table 65-2). In two open-label extension studies (Findling *et al.* 2004; Turgay *et al.* 2002), risperidone's effects were noted within the first 2 weeks of treatment and were sustained. There have also been multiple studies of adults with IDD taking risperidone to address unspecified behavioral symptoms, which showed some positive effects over placebo as measured by improvements in the Aberrant Behavior Checklist (ABC) and Clinical Global Impression (CGI) Scale (Gagiano *et al.* 2005; Vanden Borre *et al.* 1993). In a 48-week open-label follow-up, there was ongoing response and some additional improvement (Gagiano *et al.* 2005). However, increased appetite and weight gain with risperidone are common (Hellings *et al.* 2006) and can be a substantial clinical concern. Olanzapine was also found in open-label studies to decrease aggression and agitation (Handen and Hardan 2006; Janowsky *et al.* 2003a) and was also associated with significant weight gain. Aripiprazole decreased CGI scores in a retrospective chart review, although the sample also included individuals with comorbid ASD (Hellings *et al.* 2011). In contrast, one RCT has called into question the role of medications in treating behavior dysregulation in adult patients with IDD. In a comparison of haloperidol, risperidone, and placebo in the treatment of aggressive behaviors, symptoms decreased substantially by 4 weeks across all treatment arms, but the placebo group showed the greatest improvement (Tyrer *et al.* 2008), a finding possibly underscoring the role of caregiver perceptions of symptomatic behavior and how such perceptions may cloud a true understanding of psychopharmacological response in this population. Overall, existing research is extremely limited, especially in regard to long-term use of antipsychotic medication in the multimodal treatment of individuals with IDD (Deb and Unwin 2007; Duggan and Brylewski 1999; Singh *et al.* 2005).

TABLE 65-2. Summary of risperidone randomized controlled trials (RCTs): psychopharmacological studies of agitation and "problem behavior" in children and adults with intellectual developmental disorder

RCTs	Risperidone dosing range	Side effects[a]	Outcomes
Children			

Note. All RCTs had at least 10 participants/subjects. ABC = Aberrant Behavior Checklist; CGI = Clinical Global Impression Scale; EPS = extrapyramidal side effects; NCBRF = Nisonger Child Behavior Rating Form.

[a] Commonly reported side effects in studies. List is not comprehensive.

RCTs	Risperidone dosing range	Side effects[a]	Outcomes
Aman *et al.* 2002	0.4-4.0 mg/day or 0.01-0.06 mg/kg/day or 0.01-0.09 mg/kg/day (Van Bellinghen and De Troch 2001)	Weight gain, sedation, elevated serum prolactin, mild or no significant EPS	Decreased disruptive behavior (e.g., aggression) and improvement on ABC or CGI (Aman *et al.* 2002; Buitelaar *et al.* 2001; Hellings *et al.* 2006; Van Bellinghen and De Troch 2001; Vanden Borre *et al.* 1993; Zarcone *et al.* 2001)
Buitelaar *et al.* 2001	4-12 mg/day (Vanden Borre *et al.* 1993)		Improvement on NCBRF (Aman *et al.* 2002; Snyder *et al.* 2002)
Hellings *et al.* 2006			
Snyder *et al.* 2002			
Van Bellinghen and De Troch 2001			
Vanden Borre *et al.* 1993			

Note. All RCTs had at least 10 participants/subjects. ABC = Aberrant Behavior Checklist; CGI = Clinical Global Impression Scale; EPS = extrapyramidal side effects; NCBRF = Nisonger Child Behavior Rating Form.

[a] Commonly reported side effects in studies. List is not comprehensive.

RCTs	Risperidone dosing range	Side effects[a]	Outcomes
Zarcone *et al.* 2001			
Adults			
Gagiano *et al.* 2005	1-4 mg/day	Sedation, elevated serum prolactin, weight gain	Improvement in disruptive behavior based on ABC and CGI scores
Hellings *et al.* 2006	4-10 mg/day (Vanden Borre *et al.* 1993)		
Vanden Borre *et al.* 1993			
Zarcone *et al.* 2001			

Note. All RCTs had at least 10 participants/subjects. ABC = Aberrant Behavior Checklist; CGI = Clinical Global Impression Scale; EPS = extrapyramidal side effects; NCBRF = Nisonger Child Behavior Rating Form.

[a] Commonly reported side effects in studies. List is not comprehensive.

Other Medications

Medications such as SSRIs, naltrexone, buspirone, and anticonvulsants have also been examined in small, typically open-label studies of aggressive behaviors in IDD. While the evidence base is limited and derives mostly from decades-old investigations, the putatively more benign side-effect profiles of some of these agents warrant additional investigation in future research.

In an underpowered RCT (*n* = 8), clomipramine demonstrated significant reduction in frequency of SIBs (Lewis *et al.* 1996), although it did not separate from placebo, which also demonstrated a decrease in symptoms. Clomipramine was also found to reduce stereotypies and repetitive behaviors in a similar placebo-controlled, but again underpowered, RCT (Lewis *et al.* 1995).

Studies of SSRIs are quite mixed and generally lack rigorous study designs; one retrospective review found that paroxetine reduced SIBs but not aggression (Janowsky *et al.* 2005), while another demonstrated short-term improvements in aggression after 1 month, which were not sustained at 4-month follow-up (Davanzo *et al.* 1998). Improvement in SIBs was also noted with fluoxetine (Cook *et al.* 1992; Markowitz 1990) and sertraline (Hellings *et al.* 1996), although, again, these older studies were typically small and lacked a control arm. In contrast, other studies have demonstrated a mixed response to fluoxetine or paroxetine, or even a worsening of symptoms (Branford *et al.* 1998; Troisi *et al.* 1995). Despite the lack of large RCTs of SSRIs in the treatment of IDD, the relatively benign side-effect profile of SSRIs (relative to antipsychotics) indicates that empirical use of SSRIs, with careful titration and monitoring, may be of benefit in treating underlying anxiety or obsessive-compulsive symptoms (Sohanpal *et al.* 2007) as well as mood symptoms.

Mood-stabilizing medications may have a possible role in treating aggression and problem behaviors, with older controlled studies of lithium (Craft *et al.* 1987) and topiramate (Reid *et al.* 1981) demonstrating consistent improvements in target symptoms. Small retrospective studies similarly found reductions in aggression, SIBs, and challenging behaviors with lithium (Langee 1990), divalproex (Ruedrich *et al.* 1999), and topiramate (Janowsky *et al.* 2003b). Notably, individuals with IDD and comorbid epilepsy are often excluded from studies, despite the fact that seizure disorders are prevalent in this population. Interestingly, one retrospective study found decreased prescribing of antidepressants and anxiolytics for individuals with IDD who were taking antiepileptic drugs (Leunissen *et al.* 2011), although this was an observational study that requires additional investigation. Several placebo-controlled RCTs have also assessed naltrexone in IDD, with the smaller trials (4-8 participants) reporting some reduction in SIBs (Sandman *et al.* 1990, 2000; Symons *et al.* 2001; Thompson *et al.* 1994), while a larger study with 25 individuals with IDD reported no benefit; of note, this study included individuals with a milder range of symptoms (Willemsen-Swinkels *et al.* 1995).

Psychopharmacological Management of ADHD and Disruptive Behavior Disorders

Symptoms related to hyperactivity, impulsivity, and poor focus and attention are common presenting symptoms in IDD; however, most psychopharmacology research in ADHD routinely excludes children with IDD. Table 65-3 presents a summary of RCTs examining psychopharmacological treatment of disruptive behavior and ADHD in children with IDD.

TABLE 65-3. **Summary of randomized controlled trials (RCTs): psychopharmacological studies of disruptive behavior and ADHD in children with intellectual developmental disorder**

Medication/RCTs	Dosing range	Side effects	Outcomes
Methylphenidate			
Aman *et al.* 1991	0.3-1.5 mg/kg	Sleep problems with higher dosages	Aman *et al.* 1991: Improvement in specific metrics of behavioral tasks (Continuous Performance Test, matching-to-sample task, and short-term memory task)

Medication/RCTs	Dosing range	Side effects	Outcomes
Aman *et al.* 1993	Simonoff *et al.* 2013: individually titrated from 0.5 to 1.5 mg/kg	Poor appetite with higher dosages	Aman *et al.* 1993: Improvement in teacher ratings on CTRS and ABC; parent ratings showed improvement on RBPC, ABC, Real Life Rating Scale, and Global Rating Scales
Aman *et al.* 1997		Handen *et al.* 1999: Adverse side effects (including social withdrawal, crying, and irritability) noted in 5 of the 11 children in study	Aman *et al.* 1997: No improvements in parent ratings; teacher ratings showed significant improvement on ABC-Hyperactivity subscale and CTRS-Hyperactivity subscale
Aman *et al.* 2003			Aman *et al.* 2003: Improvement in teacher ratings on CTRS, ABC, and CASQ and in parent ratings

Medication/RCTs	Dosing range	Side effects	Outcomes
			on RBPC, ABC, and CASQ
Green *et al.* 2011[a]			Green *et al.* 2011: Improvement on CPRS-Revised
Hagerman *et al.* 1988			Hagerman *et al.* 1988: Teacher ratings showed improvement on ACTeRS Social Skills and Attention subscales; improvement on Conners' Abbreviated Parent-Teacher Questionnaire was not statistically significant
Handen *et al.* 1990			Handen *et al.* 1990, 1992: Improvement on CTRS and Child Attention Problems (CAP) Behavior Checklist
Handen *et al.* 1992			Handen *et al.* 1999: Improvement on CTRS and

Medication/RCTs	**Dosing range**	**Side effects**	**Outcomes**
			Preschool Behavior Questionnaire
Handen *et al.* 1999			Pearson *et al.* 2003: Significant improvements largely in teacher reports on CTRS and ACTeRS; parent report showed improvement only on CPRS Impulsive-Hyperactive subscale
Pearson *et al.* 2003			Simonoff *et al.* 2013: Improvement on CTRS, CPRS, and ABC
Simonoff *et al.* 2013			
Dextroamphetamine			
Hagerman *et al.* 1988[b]	0.2 mg/kg/day	Mood lability, irritability	Hagerman *et al.* 1988: Inconclusive--measures[b] demonstrated trends toward improvement but

Medication/RCTs	Dosing range	Side effects	Outcomes
			changes were not statistically significant
Clonidine			
Agarwal *et al.* 2001	4-8 mcg/kg/day divided bid or tid	Drowsiness, dry mouth, anorexia, dose-dependent drop in systolic blood pressure	Agarwal *et al.* 2001: Dose-related response in hyperactivity, impulsivity, and inattention via Parent Symptom Questionnaire and clinician ratings on Hillside Behavior Rating Scale
Guanfacine			
Handen *et al.* 2008	Handen *et al.* 2008: 2.5-3 mg/day divided tid	Drowsiness, irritability	Handen *et al.* 2008: Improvement on Hyperactivity subscale of Parent and Teacher ABC and on global improvement ratings
Scahill *et al.* 2015[c]	Scahill *et al.* 2015: Extended-release		Scahill *et al.* 2015: Reductions in hyperactivity, impulsivity, and

Medication/RCTs	Dosing range	Side effects	Outcomes
	formulation 1-4 mg/day		distractibility on ABC and CGI
Risperidone			
Aman *et al.* 2004	Aman *et al.* 2004: 0.02-0.06 mg/kg/day	Weight gain, hyperprolactinemia, somnolence	Aman *et al.* 2004: Risperidone plus stimulant produced better control of hyperactivity compared with risperidone alone; reductions seen in hyperactivity and disruptive behavior (via NCBRF, ABC) regardless of concomitant stimulant use
Correia Filho *et al.* 2005	Correia Filho *et al.* 2005: 2.9 mg/day		Correia Filho *et al.* 2005: Reductions seen in hyperactivity, impulsivity, and inattention via SNAP-IV, NCBRF, SERS, and UKU

Medication/RCTs	Dosing range	Side effects	Outcomes

Notes. All RCTs had at least 10 participants/subjects. ABC = Aberrant Behavior Checklist; ACTeRS = ADD-H Comprehensive Teacher Rating Scale; ASD = autism spectrum disorder; CASQ = Conners' Abbreviated Symptom Questionnaire; CGI = Clinical Global Impression scale; CPRS = Conners' Parent Rating Scale; CTRS = Conners' Teacher Rating Scale; NCBRF = Nisonger Child Behavior Rating Form; RBPC = Revised Behavior Problem Checklist; SERS = Barkley's Side Effect Rating Scale; SNAP-IV = Swanson, Nolan and Pelham IV; UKU = Udvalg for Kliniske Undersogelser Rating Scale.

[a] Green *et al.* 2011: Cohort included children with velocardiofacial syndrome.

[b] Hagerman *et al.* 1988 (Dextroamphetamine): Fragile X syndrome cohort. Teachers and parents completed Conners' Abbreviated Parent-Teacher Questionnaire; teachers also completed ACTeRS.

[c] Scahill *et al.* 2015: Cohort included children on autism spectrum with varying range of intellectual ability.

Stimulant Medications

The largest RCT of methylphenidate among children with IDD (*N* = 122 participants ages 7-15 years who were not on already on medications) found methylphenidate to be effective in about 40% of children with an ICD-10 diagnosis of hyperkinetic disorder, with an effect size of 0.39-0.52 (Simonoff *et al.* 2013), which is consistent with findings in previous RCTs in youths with IDD (Aman *et al.* 2003; Pearson *et al.* 2003) but is lower than findings reported for typically developing children (Cortese *et al.* 2018). Methylphenidate's adverse effects in children with IDD and ADHD--primarily appetite suppression and sleep problems--were similar to those in typically developing children (Pearson *et al.* 2003; Simonoff *et al.* 2013). The smaller aggregated studies in the Aman *et al.* (2003) study suggest that lower IQ might predict poorer response to methylphenidate, but the larger Simonoff *et al.* (2013) study did not find the efficacy of methylphenidate to be moderated by IQ, presence of autistic symptoms, or severity of ADHD symptoms. This suggests that despite showing smaller effect sizes in IDD, methylphenidate can be considered an efficacious treatment for ADHD across levels of severity or ASD comorbidity. Notably, studies used primarily the immediate-release formulations of methylphenidate rather than the long-acting formulations more commonly used in current practice, and evidence on amphetamine derivatives was lacking (Thomson *et al.* 2009).

RCTs also have shown that risperidone reduces hyperactivity in children with IDD and DBDs (Aman *et al.* 2002; Snyder *et al.* 2002), although these were add-on trials and permitted ongoing stimulant medication in youths with ADHD (see Table 65-3). A post hoc analysis selecting patients with ADHD (rather than unspecified DBDs) suggested that adding risperidone to a stimulant led to improved control of hyperactivity compared with stimulant use alone. In a comparison study of risperidone and methylphenidate for treatment of ADHD, both medications were found to reduce inattention and hyperactivity, in addition to oppositional defiant disorder symptoms, with more pronounced effects for risperidone (Correia Filho *et al.* 2005). Finally, Handen and Hardan (2006) found improvement in hyperactivity with olanzapine, with concomitant stimulant use allowed. Despite the potential efficacy of atypical antipsychotics for the treatment of ADHD, methylphenidate remains the first-line agent because of its more benign side-effect profile (Correia Filho *et al.* 2005).

In contrast to findings in pediatric populations, evidence for stimulant use in adult patients with IDD is largely absent, although one retrospective chart review of 10 adult outpatients with IDD and ADHD who were treated with either amphetamine or methylphenidate found that 5 (50%) of the adults demonstrated improvement in symptoms, as assessed by decreases in scores on the CGI and on the Hyperactivity and Irritability subscales of the ABC (Jou *et al.* 2004).

Nonstimulant Medications

A large open-label prospective examination of atomoxetine (Fernandez-Jaen *et al.* 2013) in 24 patients with DSM-IV (American Psychiatric Association 1994) pervasive developmental disorder and symptoms of

ADHD found significant improvement in CGI, ADHD Rating Scale IV, and Conners Ratings Scale scores, although a separate retrospective chart review suggested that response in these populations may be less robust than that in typically developing peers (Mazzone *et al.* 2011).

a-Agonists have also been studied; an RCT of clonidine (Agarwal *et al.* 2001) for children with IDD and ADHD demonstrated significant benefit on parent and clinician ratings of hyperactivity, impulsivity, and inattention. Data for guanfacine are inconclusive, with one RCT (Handen *et al.* 2008) and one retrospective chart review (Posey *et al.* 2004) demonstrating improvements in some individuals with IDD and comorbid ASD, although lack of independent analyses for cohorts without ASD comorbidity prevented meaningful interpretation for IDD.

Pharmacological Management of Disordered Sleep

Persistent sleep problems have been reported at much higher rates in individuals with IDD than in the general population (Harper *et al.* 2023). Etiologies are likely heterogeneous, but sleep disorders have consistently been identified in individuals with idiopathic IDD (Esbensen and Schwichtenberg 2016) as well as those with specific genetic syndromes (Agar *et al.* 2021). A number of RCTs have examined the efficacy of melatonin for sleep disturbances in children (Appleton *et al.* 2012; Camfield *et al.* 1996; Coppola *et al.* 2004; Dodge and Wilson 2001; Wasdell *et al.* 2008) and adults (Braam *et al.* 2008) with IDD (Table 65-4). The majority of these studies confirmed the efficacy of melatonin at standard dosages in reducing sleep onset latency and duration of total sleep, although improvement in midcycle awakening was found only with adults. In contrast to the robust literature on melatonin, there are limited studies examining other pharmacological interventions for sleep in IDD, despite their wide prevalence of use (Bruni *et al.* 2018). Medications empirically used for sleep in IDD include the broad prescription of antihistamines, clonidine, benzodiazepines and other GABAergic agents, trazodone, mirtazapine, tricyclic antidepressants, and atypical antipsychotics, which have been comprehensively reviewed elsewhere (Bruni *et al.* 2018; Hollway and Aman 2011). Given the lack of rigorous evaluation of their use to improve sleep in IDD, it is difficult to assess the clinical efficacy of these agents; however, a small number of retrospective chart reviews and open-label studies suggested that some of these medications showed possible benefit for insomnia in children with IDD. These small studies included examinations of clonidine at dosages of 0.15-0.225 mg daily (Ingrassia and Turk 2005), mirtazapine at dosages of 7.5-45 mg daily in a cohort with mixed diagnoses and clinical outcomes (Posey *et al.* 2001), and gabapentin at dosages averaging 5-15 mg/kg (Robinson and Malow 2013). Although these medications warrant future study, in the absence of other evidence, mirtazapine, gabapentin, and trazodone may be considered for insomnia that does not respond to melatonin. Clonidine may also be considered as a potential intervention if there are no contraindications to its use, with careful monitoring for side effects.

TABLE 65-4. Summary of randomized controlled trials (RCTs): psychopharmacological studies of melatonin for disordered sleep in children and adults with intellectual developmental disorder

RCTs	Dosing range	Side effects	Outcomes	Comments
Children				
Appleton *et al.* 2012	0.5-12 mg (most commonly 3-5 mg)	None reported	Improved sleep	Wirojanan *et al.* 2009: Cohort included children with ASD

Note. All RCTs had at least 10 participants/subjects. ASD = autism spectrum disorder.

RCTs	Dosing range	Side effects	Outcomes	Comments
				and fragile X syndrome
Braam *et al.* 2008	Wasdell *et al.* 2008: Active agent was controlled-release melatonin 5-15 mg			
Coppola *et al.* 2004				
Dodge and Wilson 2001				
Wasdell *et al.* 2008				
Wirojanan *et al.* 2009				
Adults				
Braam *et al.* 2008	5 mg	None reported	Decreased sleep latency, advanced mean sleep onset time, increased total sleep time, reduced number of night awakenings, and advanced dim-	Cohort included children and adults (ages 2-78 years)

Note. All RCTs had at least 10 participants/subjects. ASD = autism spectrum disorder.

RCTs	Dosing range	Side effects	Outcomes	Comments
			light melatonin onset	

Note. All RCTs had at least 10 participants/subjects. ASD = autism spectrum disorder.

Psychopharmacological Management of Mood and Anxiety Disorders

Despite early literature suggesting lower rates of mood and anxiety disorders among individuals with IDD, more recent literature indicates that the prevalence of these disorders, including major depressive disorder and anxiety disorders (Cooper *et al.* 2007; Platt *et al.* 2019), is similar to or higher than that among individuals without IDD. Yet little research has directly examined the treatment of mood disorders, anxiety disorders, OCD, or PTSD in individuals with IDD, as evidenced by the absence of large RCTs and few open-label trials. This lack of studies again raises concern for underdiagnosis of mood and anxiety disorders in individuals with IDD, as well as raising additional questions about the frequent prescription of antipsychotics and mood stabilizers in this population, rather than antidepressant and antianxiety medication. While there is a broader literature examining the use of antipsychotics and mood stabilizers in the management of disruptive, self-injurious, and challenging behaviors (outlined earlier in this chapter) that may support the tolerability and potential efficacy of these medications for the treatment of bipolar disorder in this population, rigorous RCTs examining first-line treatments in IDD for unipolar depression and anxiety disorders (i.e., SSRIs and SNRIs) are sorely needed. In addition, several small open-label studies of SSRIs have reported positive effects on specific depression outcome measures in adults with IDD, including improvement in CGI ratings and remission over a year with citalopram (average dosage 20-40 mg/day) (Verhoeven *et al.* 2001) and reduction in Hamilton Rating Scale for Depression scores with fluoxetine (average dosage 20-40 mg/day) (Howland 1992). Paroxetine (average dosage 20-40 mg/day) was also found to reduce Montgomery-Asberg Depression Rating Scale scores in adolescents with mild IDD and comorbid major depressive disorder (Masi *et al.* 1997). Specific to OCD, one open-label study in adults found improvement in target symptoms with fluoxetine (40-80 mg/day) (Bodfish and Madison 1993), and another noted improvement with clomipramine (75 mg/day) (Barak *et al.* 1995). There is a dearth of research on well-defined bipolar disorder in this population, although small studies have indicated benefit from valproic acid in adults and adolescents (Kastner *et al.* 1993; King *et al.* 2000). Data for lithium and carbamazepine are limited to case reports, and outcomes are mixed (Vanstraelen and Tyrer 1999).

Given the lack of robust evidence, psychopharmacological approaches may be extrapolated from the broader literature in typically developing populations, with careful consideration for adverse side effects and judicious diagnostic consideration to avoid overdiagnosis of bipolar and psychotic disorders (Charlot *et al.* 2007). Additionally, RCTs of SSRIs, serotonin-norepinephrine reuptake inhibitors, and mirtazapine for the treatment of mood and anxiety disorders in individuals with IDD are much needed, especially because their long-term tolerability and favorable side-effect profiles make these medications good options.

Psychopharmacological Management of Schizophrenia and Schizoaffective Disorder

The prevalence of schizophrenia spectrum disorders is higher in individuals with IDD (2%-7%) relative to the general population (Deb *et al.* 2001; Cooper *et al.* 2007; Morgan *et al.* 2008). However, the extent to which this difference represents shared etiological factors, overdiagnosis, evidence of premorbid intellectual deficits in schizophrenia spectrum disorders, or intellectual decline associated with onset of schizophrenia in adulthood is still unclear. Regardless of etiology, prevalence rates do not appear to match with prescription practices; a recent UK study that analyzed treatment data for adults with IDD who had received antipsychotic medication for at least 1 year ($N = 977$) found that 24% of these individuals were prescribed this medication for a diagnosis of a schizophrenia spectrum disorder, a much higher rate than expected (Paton *et al.* 2022). When an accurate diagnosis of schizophrenia is determined, efficacy of antipsychotic usage specific to IDD is unknown (Duggan and Brylewski 1999), and decision-making relies largely on clinical judgments from the broader schizophrenia evidence base. One clinical consideration is that psychosis in individuals with IDD may be associated with greater symptom burden and more severe negative symptoms compared with psychosis in individuals with schizophrenia without IDD (Bouras *et al.* 2004). Additionally, careful consideration regarding seizure risk should be incorporated in treatment decision-making, particularly for medications such as clozapine (Ayub *et al.* 2015).

Recent Research in Genetic Syndromes

Routine clinical workup for newly diagnosed IDD should include referral for genetic testing (Muhle *et al.* 2017), because the diagnostic yield for specific genetic syndromes is increasing (Anazi *et al.* 2017). IDD is a nonexclusive diagnosis, which means that concurrent diagnoses of IDD and an identified genetic syndrome or medical condition associated with IDD (e.g., fragile X syndrome [FXS]) are appropriate. Given the expansion of genetic testing and identification of IDD-associated genes, it is expected that the cohort of identified genetic syndromes in IDD will increase in the coming years, although nonsyndromic etiologies continue to be the largest cohort in IDD at this time. Although this chapter has focused on idiopathic or nonsyndromic IDD, there are several studies on pharmacological approaches that may be appropriate for consideration in syndromic IDD, because individual genetic syndromes have specific behavioral phenotypes that may benefit from syndrome-specific intervention, including medication management. It would be difficult to comprehensively review the broader literature, but a few studies are highlighted here. Additionally, the putatively more homogeneous etiologies underlying IDD in these syndromes may provide important mechanistic insights into IDD symptoms and behaviors more broadly.

Fragile X Syndrome

The bulk of pharmacological research on genetic syndromes in IDD exists in the FXS literature. FXS is the most common inherited cause of IDD, resulting from a trinucleotide repeat in the *FMR1* promoter region, occurring in about 1 in 7,000 boys and 1 in 11,000 girls (Hunter *et al.* 2014). Comorbid psychiatric conditions are commonly associated with FXS, including ASD, anxiety, inattention, hyperactivity, irritability, and aggression. Unsurprisingly, the medications prescribed for management of these symptoms are similar to those prescribed in idiopathic IDD, including SSRIs, psychostimulants, and atypical antipsychotics, with generally positive response rates for target symptoms (Dominick *et al.* 2021; Erickson *et al.* 2011). Specific to FXS, neurobiological treatment targets have focused on metabotropic glutamate and GABA receptors, based on downstream effects of the FMR protein. However, despite promising drug investigations in animal studies, similar studies in human clinical trials targeting these pathways have generally not yielded positive results in primary outcomes, although this remains a robust area of ongoing research (Berry-Kravis *et al.* 2018; Hagerman *et al.* 2017). Also, a large RCT was conducted with minocycline for children with FXS, demonstrating improvement in CGI and mood and anxiety scores (Leigh *et al.* 2013). Targeting aberrant Ras/MAPK activity in FXS, both a small, open-label

trial of lovastatin (Caku *et al.* 2014) and a combination RCT of minocycline and lovastatin (Champigny *et al.* 2022) demonstrated improvements in ABC Community scores. Also, small case studies (Biag *et al.* 2019; Dy *et al.* 2018; Protic *et al.* 2019) and an open-label trial (Proteau-Lemieux *et al.* 2021) have suggested potential benefit with metformin. Transdermal cannabidiol in a cohort of 20 youths with FXS and anxiety demonstrated decreases on the Anxiety, Depression and Mood Scale over a 12-week period (Heussler *et al.* 2019), although IQ was not included in demographic data or inclusion criteria. Data on nutraceuticals, such as folic acid and L-acetylcarnitine, are equivocal in human studies (Rueda *et al.* 2011, 2015).

Other Genetic Syndromes

Rigorous placebo-controlled studies specific to other genetic syndromes associated with IDD are also lacking. Again, pharmacological approaches largely approximate approaches in idiopathic IDD (Butler *et al.* 2006; Palumbo and McDougle 2018; Sabus *et al.* 2019). Here, selective reviews of medication trials in syndromes are highlighted, as well as some discussion of drug development that may have potential future impact on IDD more broadly.

In Down syndrome, for example, acetylcholinesterase inhibitors have been studied as a potential intervention for dementia in older individuals with Down syndrome and in RCTs in children and adolescents (Kishnani *et al.* 2010; Spiridigliozzi *et al.* 2016). Unfortunately, results did not show a significant impact on cognitive, language, and adaptive functioning, but treatment was well tolerated. As in nonsyndromic IDD, low dosages of guanfacine were found to reduce hyperactivity and irritability symptoms in children with Down syndrome and comorbid ADHD, the majority of whom were not taking stimulants (Capone *et al.* 2016).

In Rett syndrome, recent research has focused on clinical trials of trofinetide, a synthetic insulin-like growth factor analog that has shown promising results based on CGI and Rett Syndrome Behavior Questionnaire scores (Glaze *et al.* 2019), including recent positive industry-funded Phase III trial outcomes (Neul *et al.* 2023). Based on these studies, trofinetide received FDA approval in March 2023 for the treatment of Rett syndrome in adults and pediatric patients ages 2 years and older. Trofinetide and similar agents are preliminarily being assessed in other conditions, such as FXS.

An RCT in Prader-Willi syndrome targeting perseverative eating behaviors demonstrated reductions in hyperphagia with topiramate (Consoli *et al.* 2019), although no between-group differences were found in CGI scores. Several recent RCTs of oxytocin administration in Prader-Willi syndrome have also shown improvements in mood and in social and eating behaviors (Damen *et al.* 2021; Kuppens *et al.* 2016; Miller *et al.* 2017). Open-label studies have also suggested potential limited benefit of *N*-acetylcysteine in skin-picking behaviors in Prader-Willi syndrome (Miller and Angulo 2014; Wieting *et al.* 2022).

Although studies in syndromic IDD are limited and there is still incomplete understanding of how pharmacological interventions may be extrapolated from one condition to another, the mechanistic models for aberrant neurodevelopment in syndromic IDD may also provide a model for hypothesis-driven approaches to drug development for idiopathic IDD more broadly. A road map for translational research initiatives that may lead to innovation in IDD treatment is sorely needed (Markati *et al.* 2021; Vashi and Justice 2019) and would fill a critical gap in treatment development for nonsyndromic IDD.

Medication Side-Effect Profiles

Until disease-modifying treatments are available, treatment of comorbid or nonspecific symptoms remains the primary clinical intervention in IDD. With this in mind, addition of medications requires thoughtful and ongoing evaluation for actual benefit for target symptoms balanced against vigilant monitoring for adverse side effects. Careful attention to side effects is particularly relevant in IDD, where complex cases often result in substantial polypharmacy, further increasing the potential risk of drug-drug interaction effects and adverse events. A recent cross-sectional study of youth and adolescents with IDD ($N = 1{,}333$; ages 5-21 years; included youth with ASD) found that more than 86% of the sample received psychotropic medications, and more than half were on three or more psychotropics (McLaren *et al.* 2021).

Reducing the likelihood of adverse side effects and identifying them when they do manifest are especially important for vulnerable IDD cohorts; this is particularly true for individuals with limited communication, placement in living environments with less supervision, decreased ability to self-advocate, or limited access to appropriate specialized care. For example, sedating and cognitive impairment effects should be considered in pharmacological treatment selection for individuals with baseline cognitive deficits, as may occur with anticholinergic and antihistaminergic agents. Concern for long-term weight gain should also be considered when starting antipsychotics, especially given evidence of challenges in regular monitoring of metabolic side effects on an ongoing basis (Teeluckdharry *et al.* 2013). Indeed, logistical challenges, such as difficulty obtaining labs, may also be a consideration for medications that require frequent monitoring (e.g., clozapine, lithium). Similarly, as epilepsy is overrepresented in IDD, agents lowering the seizure threshold may be inadvisable--although, conversely, use of mood stabilizers or antiepileptic drugs may present an opportunity for parsimonious treatment decisions given their dual clinical functions.

While the increased representation of adverse side effects in IDD is probably due to both direct and indirect mechanisms, these effects do appear to be observed at higher rates than would be expected in comparable populations. Common side effects with higher-than-expected rates in individuals with IDD include gynecomastia, EPS, hyperprolactinemia, hypercholesterolemia, and akathisia (Ballester *et al.* 2022; Charlot *et al.* 2020; Sheehan *et al.* 2017). Clinical signs of EPS in this population may include staring, flat facial expression, prolonged response latency, odd facial grimacing, tremors, and muscle stiffness, which clinicians may mistake for features of IDD (i.e. diagnostic overshadowing), thereby missing serious medication side effects. For example, akathisia may be mistaken for an increase in impulsivity, agitation, or restlessness, especially in an individual with limited language to share internalizing experiences, possibly leading to an increase in medications rather than the needed dosage tapering. Rates of serious adverse side effects with antipsychotic medication are also increased in this population; for example, antipsychotic-related neuroleptic malignant syndrome is three times more common in adults with IDD than in control subjects without IDD (Sheehan *et al.* 2017).

Therefore, de-prescription practices are particularly relevant in pharmacological management of IDD, because it is a pervasive, lifelong condition. Indeed, it is not uncommon for individuals with IDD to accumulate multiple psychotropic medications over years of treatment. Rigorous approaches to de-prescription can be drawn from parallels in other cohorts, such as medication management in older adults (Scott *et al.* 2015), and have been modeled in health systems in other countries where treatment philosophies for individuals with IDD focus more heavily on wraparound services and minimization of antipsychotic use to control aggression (Granas *et al.* 2019; Shankar *et al.* 2019a). Generally, deprescribing should follow rational risk-benefit assessment at regular intervals during treatment of individuals with IDD (Scott *et al.* 2015; Shankar *et al.* 2019b), via an interdisciplinary approach incorporating all stakeholders, particularly caretakers of the individuals with IDD (Ahmed *et al.* 2000; de Kuijper and Hoekstra 2018).

Conclusion

The research base for pharmacological intervention in IDD is limited. Careful diagnosis and identification of specific treatment targets are needed in this vulnerable population. When present, specific comorbid diagnoses should be treated, often with pharmacological interventions for anxiety, mood disorders, ADHD, and psychosis similar to those used with non-IDD cohorts. Nonspecific diagnoses, such as challenging or problem behaviors, remain a common presentation in IDD, and atypical antipsychotics are often prescribed for these symptoms. However, the existing evidence indicates that these medications confer only modest benefits and often carry a substantial side-effect burden, highlighting the need for comprehensive, multimodal approaches in IDD that encompass behavioral and systems-of-care interventions rather than relying on pharmacotherapy alone. Therefore, treatment selection in IDD requires rational assessment of the need for each medication weighed against potential drug-induced harm, with ongoing careful monitoring of actual benefit and potential adverse side effects. Given the long-term nature of IDD, comorbid symptoms and behaviors should be routinely assessed, and de-prescription of medication for these symptoms should be considered at regular intervals in the treatment process.

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CHAPTER 66

Treatment of Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent challenges in social communication and social interaction and the presence of a range of sensory processing differences and restricted and repetitive behaviors (RRB). As outlined in DSM-5 (American Psychiatric Association 2013) and ICD-11 (World Health Organization 2018), ASD symptoms must present early in life but may be masked or not fully manifest until demands exceed a child's capacity or learned strategies. The core social communication impairments (SCI) and RRB symptoms of ASD are usually pervasive and observable across multiple settings, with some variation depending on context, and must be severe enough to cause clinically significant impairments in personal, social, educational, occupational, or other important areas of functioning for the child to meet diagnostic criteria. Autistic individuals may or may not also exhibit additional cognitive and behavioral challenges, such as intellectual developmental disorders, adaptive skill deficits, language delay, or a multitude of other comorbid psychiatric symptoms and medical issues, including anxiety, depression, attentional problems, epilepsy, sleep disturbances, and gastrointestinal issues. Recent prevalence rates for ASD range from 1 in 36 children in the United States (Maenner *et al.* 2023) to approximately 1 in 161 individuals worldwide (Elsabbagh *et al.* 2012), with an estimated yearly economic cost of up to $1 trillion just in the United States (Leigh and Du 2015). Although ASD is a pervasive developmental disorder, our understanding of its underlying pathophysiology is still very incomplete, and there are currently no biologically based pharmacological interventions for targeting the core symptom domains. Behavioral therapy is typically the first-line treatment for patients with ASD, and pharmacological interventions are currently directed at the management of comorbid psychiatric and medical conditions, with the primary goal of improving functioning in daily activities.

This chapter will review the history of drug trials in patients with ASD, discuss current clinical practices and novel agents that are under investigation, and outline recommendations and future directions for targeting the core symptom domains.

Brief History of Drug Trials in Autism Spectrum Disorder

Failed Randomized, Placebo-Controlled Trials for Core Symptoms

Serotonergic Agents

Shortly after the first descriptions of autistic patients by Leo Kanner (Kanner 1943) and Hans Asperger (Asperger 1944), research to elucidate the biochemical basis of the disorder began. One of the earliest studies examined whole blood levels of serotonin and reported that 6 of 23 patients with "infantile autism" were well outside the normal range (Schain and Freedman 1961). Subsequent studies of the potential role of serotonin in autism have reported mixed results, yet a recent meta-analysis indicated that both whole blood and platelet-rich plasma levels are consistently elevated in approximately 25% of individuals diagnosed with ASD (Gabriele *et al.* 2014). Following these initial reports, small-scale trials investigating the potential efficacy of serotonergic drugs, particularly selective serotonin reuptake inhibitors (SSRIs) for targeting RRB, were initiated because SSRIs were previously shown to be effective for targeting compulsive and repetitive behaviors in other disorders such as OCD (Soomro *et al.* 2008). To date, the small number of randomized controlled trials (RCTs) that have been completed in patients with ASD indicate some potential benefits for adults, while findings in youth are inconsistent (Williams *et al.* 2013). Nonetheless, serotonergic drugs remain "a prime candidate for treatment development" in children and adults with ASD (Muller *et al.* 2016), and serotonergic biomarkers may aid in the identification of patients most likely to respond to SSRIs.

Dopaminergic Agents

In addition to SSRIs, dopaminergic agents have also received considerable attention in ASD. Autism was initially conceptualized as a childhood form of schizophrenia, in which dopaminergic dysfunction is postulated to play a central role. A dopamine hypothesis has also been proposed as a primary mechanism in ASD (Paval 2017), with both hypo-dopaminergic (Ernst *et al.* 1997) and hyper-dopaminergic (Nakamura *et al.* 2010) activity being reported. First-line treatments for schizophrenia (e.g., typical antipsychotics such as haloperidol) have high affinity for D_2 receptors and were some of the earliest pharmacological treatments that were examined for ASD. They exhibited some initial promise for targeting global improvements in emotion regulation and maladaptive behaviors, as well as some other behaviors associated with the core symptom domains (Anderson *et al.* 1984; Faretra *et al.* 1970). Further research then indicated that atypical antipsychotics may be even more effective than typical antipsychotic agents for children with ASD (Miral *et al.* 2008). However, typical and atypical antipsychotics can lead to some severe side effects in children and adolescents, including significant weight gain and tardive dyskinesia, and they are not selective for dopamine receptors. Thus, increased monitoring is necessary when antipsychotics are administered to autistic patients, and additional research will be necessary to elucidate the potential role of dopamine in the pathophysiology of the disorder, especially as it relates to treatment response and the development of more targeted interventions. Currently, the only approved drugs for use in children and adolescents with ASD are the atypical antipsychotics risperidone and aripiprazole. They are discussed in more detail later in this chapter.

Glutamatergic and GABAergic Agents

Another prominent theory regarding the pathophysiology of ASD posits that an imbalance between excitatory and inhibitory signaling underlies the core symptom presentation (Hussman 2001; Rubenstein and Merzenich 2003), specifically an increased ratio of excitation to inhibition in key neural circuits in the brain. Both glutamatergic (Moreno-Fuenmayor *et al.* 1996) and GABAergic (Dhossche *et al.* 2002) dysfunction have been implicated in ASD, but as with dopaminergic alterations, there are mixed reports regarding the specific signaling pathways and brain circuits (Fung *et al.* 2021;

Hegarty *et al.* 2018a, 2018b). Patient responses to GABAergic (Brondino *et al.* 2016) and glutamatergic (Rojas 2014) drugs are also mixed, which may be partially related to developmental changes in these systems over time and the extreme neurobiological heterogeneity across affected individuals. Early investigations suggested that glutamatergic (e.g., memantine) and GABAergic (e.g., arbaclofen) agents may provide some therapeutic effects in patients with ASD (Chez *et al.* 2007; Erickson *et al.* 2014), but the primary outcome measures on subsequent RCTs failed to replicate these early findings (Aman *et al.* 2017; Veenstra-VanderWeele *et al.* 2017). Secondary analyses of these data indicate that additional investigation may be warranted.

Other Miscellaneous Interventions

Anecdotal evidence supports a wide array of alternative therapies for targeting both core and comorbid psychiatric symptoms in children with ASD, including dietary restrictions, nutritional supplements, hyperbaric oxygen therapies, acupuncture, and massage (Brondino *et al.* 2015). Support for most of these treatments is based largely on parent reports of individual patients, case series, and open-label trials, with empirical evidence from RCTs either lacking or inconclusive. For instance, Horvath *et al.* (1998) reported in a case series that three autistic children who were given secretin for a clinical endoscopy, a hormone that regulates water homeostasis and secretions in the stomach, pancreas, and liver, exhibited improved eye contact, alertness, and expressive language after infusion (Horvath *et al.* 1998). Secretin then received considerable media coverage and interest from parents and patients that resulted in significant off-label use. Unfortunately, RCTs of secretin failed to support these initial reports, and their results indicated that secretin was unlikely to provide any cognitive or behavioral benefits for children with ASD (Sandler *et al.* 1999; Sturmey 2005). Although secretin did not benefit the core symptom domains, it did help spur investigations into the potential role of gastrointestinal disturbances in the disorder, which are common in autistic patients and a salient treatment target for some individuals (McElhanon *et al.* 2014). Alternative therapies can be attractive treatment options for parents and patients if they are generally safe and well tolerated and could potentially provide some clinical benefits, but additional RCTs will be necessary before clinicians can recommend widespread use.

Issues That Contribute to Failed RCTs

Case studies and pilot trials have reported potential efficacy for a wide array of pharmacological interventions for symptoms of ASD, but there are currently no drugs approved by the FDA or European Medicines Evaluation Agency (EMA) for targeting the core SCI and RRB. Some trials in patients with ASD fail simply because of a lack of efficacy of the investigational drug for the target symptom. However, a significant proportion of these trials may also fail due to the extreme phenotypic and biological heterogeneity across autistic individuals, changes in treatment response over different developmental periods, high levels of placebo response, increased incidence of psychiatric and medical comorbidities in the ASD population, and poor psychometric properties and sensitivity to change of the available outcome measures for assessing treatment-related change. Therefore, innovative approaches are needed, such as adaptive clinical trial designs--including sequential parallel comparison design (Fava *et al.* 2003) and its more recent extension, two-way enrichment design (Ivanova and Tamura 2015)--that aim to reduce the placebo response. Furthermore, novel platform designs (Berry *et al.* 2015) such as Leapfrog that test multiple interventions and use statistical analyses to remove poorly performing arms (Blackwell *et al.* 2019) will be necessary to account for and address the complicating and confounding factors encountered in ASD trials and will be critical for advancing the development of new pharmacological treatments for the core features, associated behaviors, and comorbid mental health disorders in this patient population.

Heterogeneity and Changes in Treatment Response Over Development

A major factor that modulates treatment response in children with ASD is the extreme heterogeneity of the disorder in terms of its pathophysiology and clinical phenotype (Jeste and Geschwind 2014; Masi *et al.* 2017), which has been well documented in the literature. First and foremost, up to 25% of cases of ASD are associated with various rare genetic and copy number variants, yet even the most prevalent individual genetic alteration is associated with only about 1% of cases. Therefore, most ASD cases probably originate from complex interactions between common multifactorial genetic variation and environmental factors (Miles 2011). These extreme differences in genetic and environmental contributions to the disorder are also reflected in the associated neurobiology (Hegarty *et al.* 2019, 2020a, 2020b), with significant alterations in brain structure, circuits, and neurochemical profiles across individuals (Amaral *et al.* 2008; McDougle *et al.* 2005a). Children and adults with ASD also display significant differences in symptom presentation across the core and comorbid psychiatric domains and exhibit a wide array of associated health and medical considerations. Developmental changes in cognitive, behavioral, and neurobiological profiles may also alter treatment response over time (Courchesne *et al.* 2011; Eaves and Ho 1996). Differences in response to fluoxetine are a prominent example of the effects that this neurobiological heterogeneity and developmental changes over time can have on treatment outcomes. For instance, most studies of fluoxetine in adults with ASD report significantly greater changes in RRB symptom severity with fluoxetine than with placebo, at least in the proportion of responders (~35%-50%) (Hollander *et al.* 2012; McDougle *et al.* 1996), whereas findings in children and adolescents are mixed (Herscu *et al.* 2020; Hollander *et al.* 2005), such that the current literature does not support widespread use of fluoxetine for children or adolescents with ASD. Fluoxetine might be beneficial for some autistic adults, but larger-scale RCTs will be necessary. Clinical research has also indicated that only about 25% of individuals with ASD exhibit hyperserotonergia, suggesting that only a proportion may respond to SSRIs. Differences in treatment response to SSRIs may also be related to genes associated with the serotonin transporter system that are altered in only a subset of the population (Sugie *et al.* 2005).

Increased Vulnerability to Side Effects

Children and adults with ASD have a high likelihood of exhibiting symptoms associated with other psychiatric disorders, especially anxiety and ADHD, and a wide array of medical and health considerations, including gastrointestinal disorders, seizures, and diabetes (Croen *et al.* 2015; Simonoff *et al.* 2008). These comorbid psychiatric, neurological, and medical conditions can create significant problems for treatment-related research because they may confer increased vulnerability to side effects from the investigational agents (McCracken 2005). For instance, studies investigating the use of methylphenidate to target symptoms of ADHD in children with ASD reported higher rates of "intolerable adverse events" (~30%) (Research Units on Pediatric Psychopharmacology Autism Network 2005) than were reported for children with ADHD only (~10%) (Wigal *et al.* 2006). Research studies have addressed this issue by excluding participants with comorbid diagnoses or using an initial dosage escalation phase to identify and exclude any participants who are not likely to respond (Sturman *et al.* 2017), but increased vulnerability to the study agents can still reduce retention of the remaining study participants. More importantly, knowledge of this increased vulnerability to certain agents alters the benefit-to-risk ratio of these agents for certain patients and may necessitate increased clinical monitoring, with regular evaluation across developmental periods.

Limitations of Primary Outcome Measures

One of the most important aspects of clinical trial design is the selection of reliable and valid outcome measures that are sensitive to treatment-related change. Objective biological markers have been identified for many medical and neurological disorders, but psychiatric research still relies heavily on subjective parent and clinician rating scales. The appendix table at the end of this chapter lists the clinical scales commonly used to monitor symptom severity in patients with ASD. To date, the assessment instruments used to measure changes in core symptom severity in clinical trials for ASD have been extremely variable across investigations, as have the psychometric properties associated with these instruments. Attempts have been made to identify the most appropriate outcome measures for trials targeting the core symptoms of ASD (Anagnostou *et al.* 2015; Scahill et al. 2015a), but there continue to be significant limitations in even the most commonly used and recommended measures. Therefore, efforts are ongoing to improve existing scales through use of factor analysis (Frazier *et al.* 2014; Sturm *et al.* 2022; Uljarevic *et al.* 2021; Zheng *et al.* 2021) and to design new scales with better construct validity and reliability (Phillips *et al.* 2019; Uljarevic *et al.* 2023). The development of more objective biological and surrogate outcome markers will also be critical for advancing pharmacological treatments for patients with ASD. Research into behavioral, physiological, and biological outcomes has already begun to report promising preliminary results (Ecker and Murphy 2014; Webb *et al.* 2020).

FDA-and EMA-Approved Treatments

Atypical Antipsychotics

The only pharmacological interventions currently approved by the FDA for use in children and adolescents with ASD are the atypical antipsychotics aripiprazole (Marcus *et al.* 2009; Owen *et al.* 2009) and risperidone (Hardan *et al.* 1996; McCracken *et al.* 2002; Sharma and Shaw 2012); however, these agents are not indicated for targeting the core symptom domains. Instead, they are used to treat symptoms of emotion dysregulation, such as severe irritability and aggression, that are associated with behavioral challenges in 20%-50% of autistic children (Lecavalier 2006; Samson *et al.* 2014), including self-injurious behaviors. Risperidone is also approved by the EMA for persistent aggression in conduct disorder in children. The target dosage for risperidone is about 1.6 mg/day (0.3-3.5 mg) and for aripiprazole is typically 5-15 mg/day. RCTs of risperidone reported greater decreases in irritability, aggression, tantrums, and self-injurious behaviors in autistic patients ages 5-17 years compared with placebo. Similarly, RCTs of aripiprazole also reported decreased irritability and some secondary effects on stereotypy, hyperactivity, and inappropriate speech, but these secondary targets still require replication in independent studies. These two atypical antipsychotics also appear to be superior to typical antipsychotics, such as haloperidol (Miral *et al.* 2008), as well as many other agents in terms of both efficacy and safety (Fung *et al.* 2016). Thus, risperidone and aripiprazole may provide some benefits in emotion regulation and help reduce some challenging or self-injurious behaviors, but it is important to implement increased monitoring for side effects because these agents are also associated with considerable adverse events, including nausea, dizziness, insomnia, increased appetite, significant weight gain, and extrapyramidal side effects (EPS) such as tardive dyskinesia.

Melatonin

Sleep disturbances are very common in children with ASD, with parent-reported sleep problems in up to 80% of autistic individuals (Couturier *et al.* 2005; Polimeni *et al.* 2005). These sleep problems are also associated with increased attentional, learning, and behavioral challenges during the day, including more severe irritability and aggression, which can be a primary source of stress for parents and caregivers and distress for patients. Meanwhile, improving sleep health with melatonin supplementation can reduce these challenging behaviors and improve overall quality of life (Schroder *et al.* 2019). Melatonin is commonly used over the counter to address sleep disturbances, and RCTs support traditional anecdotal evidence with reports of reduced time to sleep onset and increased sleep duration compared with placebo (Garstang and Wallis 2006; Rossignol and Frye 2011; Wright *et al.* 2011). Most studies evaluating melatonin (~1-10 mg) for targeting sleep in patients with ASD also report better sleep health and improved daytime behaviors with only minor side effects (e.g., morning drowsiness). New prolonged-release formulations (Circadin for adults and Slenyto for pediatric patients) have received considerable interest for improving sleep health in ASD (Gringras *et al.* 2017; Schroder *et al.* 2019). Slenyto is currently approved by the EMA for this purpose, but a clinical trial that was scheduled to begin in the United States in 2020 (NCT04233502) was canceled and withdrawn from ClinicalTrials.Gov.

Pharmacological Treatments for Specific Symptom Domains

Inattention

Before DSM-5, a diagnosis of ASD would preclude a patient from being diagnosed with ADHD (Antshel and Russo 2019), even when there were co-occurring symptoms. Comorbid diagnoses of ADHD and ASD are now common (Doernberg and Hollander 2016), with an approximate overlap of 30%-70%, yet pharmacological management of inattention and hyperactivity symptoms remains fundamentally the same for patients with a single or a dual diagnosis. Stimulants, such as methylphenidate, are the typical first-line treatment (Mahajan *et al.* 2012). However, there is only preliminary and limited evidence that methylphenidate reduces hyperactivity or inattention in children with ASD (Sturman *et al.* 2017). For instance, only about 50% of individuals with ASD may respond to methylphenidate treatment (Research Units on Pediatric Psychopharmacology Autism Network 2005), as opposed to approximately 80% of children with ADHD without concomitant ASD (Schachter *et al.* 2001). Children with ASD may also be more likely to exhibit "intolerable adverse events" during methylphenidate treatment. Thus, more conservative treatment approaches such as behavioral or environmental interventions should be explored before pharmacological therapy is initiated (McGuire *et al.* 2016). In cases where methylphenidate may be appropriate, children ages 6 years and older are typically prescribed 5 mg orally twice per day, before breakfast and lunch ("Methylphenidate" 2021; Sturman *et al.* 2017). A third dose before 6:00 P.M. can also be added, or an extended-release variant may be considered. Adults are typically prescribed 20-30 mg/day in two or three doses before meals.

In cases that are refractory to management with stimulants, alternative medications such as noradrenergic reuptake inhibitors (e.g., atomoxetine) or a_2-adrenergic agonists (e.g., clonidine or guanfacine) may be considered. However, the data pertaining to these medications are also limited in the context of ASD, and they should be trialed only as second-line pharmacological options (Banas and Sawchuk 2020; Ghanizadeh 2013; Scahill *et al.* 2015b). The following dosing recommendations were developed specifically for children with ADHD and will warrant further study in children with ASD. Atomoxetine may be prescribed to patients above the age of 6. If

they weigh 70 kg or less, the initial dosage should be 0.5 mg/kg/day, which can be increased after a minimum of 3 days to 1.2 mg/kg/day, up to a maximum of 1.4 mg/kg/day or 100 mg/day, whichever is less. Higher dosages can be considered if benefits were observed at lower dosages and no severe adverse effects events are reported. For patients above 70 kg, the initial dosage of 40 mg/day may be increased to 80 mg/day as tolerated. After another 2-4 weeks, the dosage can be further increased up to 100 mg/day ("Atomoxetine" 2021). Guanfacine is usually initiated at 1 mg/day and increased on a weekly basis by 0.5-1.0 mg, up to a maximum of 4 mg/day when well tolerated. Clonidine is generally prescribed to patients above the age of 6 years starting at 0.05 mg/day and is generally titrated up from an initial nightly dose to up to 4 times a day (Markram and Markram 2010). There is also some evidence that risperidone may reduce some symptoms of hyperactivity in children with ASD (Huffman *et al.* 2011; McCracken *et al.* 2002), but the benefit-to-risk ratio is rarely favorable for this use. When considering the best pharmacological approach for ADHD symptoms in autistic patients, it is imperative to consider all the various risks and benefits of each potential treatment. Methylphenidate and other stimulants are substances with addictive potential, a_2-adrenergic agonists can induce orthostatic hypotension, and antipsychotics have well-known adverse effects including weight gain and tardive dyskinesia.

Depression and Anxiety

Lifetime prevalence estimates of depression and anxiety in individuals with ASD range up to about 80% (Billstedt *et al.* 2005; Joshi *et al.* 2013; Nimmo-Smith *et al.* 2020; Vasa and Mazurek 2015), with meta-analyses indicating approximately 40% on average, and these estimates are at least two to three times higher than those for peers without ASD (Hollocks *et al.* 2019). Thus, the identification of depression and anxiety in patients with ASD is extremely important for their clinical care, but accurately identifying these symptoms can be difficult because cognitive and behavioral differences may lead to atypical symptom presentation, especially for nonspeaking or minimally verbal individuals or those who need a high level of support. As with most mood disorders, pharmacological therapy may be indicated in cases that are refractory to cognitive and behavioral intervention or for patients who exhibit a limited response. In patients without neurodevelopmental disorders, the guidelines for first-line medications are well supported (Bandelow *et al.* 2017; Karyotaki *et al.* 2016) and primarily include SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs). However, there is not yet sufficient evidence to support any specific guidelines regarding the use of SSRIs or SNRIs for treating depression or anxiety symptoms in individuals with ASD (Chandrasekhar and Sikich 2015; Menezes *et al.* 2020; Williams *et al.* 2013). Despite these limitations, SSRIs are still frequently prescribed (Mandell *et al.* 2008; Menezes *et al.* 2020). For instance, fluoxetine can be initiated orally (PO) in children 8 years and older at 10 mg/day to target depression. The dosage can be increased after 1 or more weeks to 20 mg/day in children and adolescents and as much as 60-80 mg/day in adults ("Fluoxetine" 2021). Escitalopram is also commonly used in children ages 7 years and older at 10-20 mg/day to target depression, initiated at 10 mg/day and increased if necessary after at least 3 weeks in children and 1 week in adults ("Escitalopram" 2021). There are also several reports describing the use of these SSRIs for anxiety (Vasa *et al.* 2014). Atypical antidepressants and anxiolytics as well as other second-line pharmacological substances, such as mirtazapine and buspirone (Chugani *et al.* 2016; Posey *et al.* 2001), also have some limited evidence, but guidelines for these agents in patients with ASD also require further study.

Research examining the presentation and treatment of depression and anxiety in patients with ASD is especially important in light of the high rate of nonsuicidal self-injury and suicidal behavior in this population. Rates have been reported to be greater than 50% for suicidal ideation and greater than 30% for suicide attempts, such that individuals with ASD may account for more than 10% of the overall suicidal population (Hedley and Uljarevic 2018; Segers and Rawana 2014). This equates to individuals with ASD being up to six times more likely to attempt suicide and seven times more likely to die by suicide compared with the general population (Chen *et al.* 2017; Hirvikoski *et al.* 2016; Kirby *et al.* 2019). Suicide is such a critical issue for people with ASD that the International Society for Autism Research recently released a policy brief calling attention to this "hidden crisis." Suicide attempts may also be more common in individuals with more severe symptoms (Hand *et al.* 2020; Hedley and Uljarevic 2018; Pelton and Cassidy 2017) or intellectual developmental disorders, and individuals with difficulties in communication or expression of internal emotional states may be more likely to progress from suicidal ideation to actual suicide attempts. Additionally, autistic women appear to be especially vulnerable and may be more than 13 times more likely to die by suicide compared with nonautistic women (Hirvikoski *et al.* 2016). Thus, it is possible that suicidal thoughts and behaviors may have a different pathophysiology in some individuals with ASD compared with the general population, and conventional prevention strategies may not be as effective (Cassidy *et al.* 2018). The Safety Planning Intervention developed by Stanley and Brown (2012) is one evidence-based prevention approach for targeting suicide that has the potential to help people with ASD who are experiencing suicidal thoughts or behaviors. Most importantly, this intervention was recently adapted for individuals with ASD and is available online free of charge (Cassidy 2019). Furthermore, this adaptation is currently being investigated as a prevention procedure specifically designed for and validated in autistic adults (Rodgers *et al.* 2023).

Restricted and Repetitive Behaviors, Obsessive-Compulsive Behaviors, and Tics

Autistic people exhibit a wide range of repetitive, obsessive, and motor behaviors. The core RRB symptoms of ASD include repetitive motor behaviors (stereotypies), insistence on sameness, self-injurious behaviors, obsessive-compulsive behaviors, and circumscribed interests. Tics are also observed in ASD and consist of sudden twitches, movements, or sounds that individuals produce repeatedly. Although RRB is a diagnostic criterion of ASD, it is important to note that OCD and tic disorders are not, even though OCD and tic disorders are reported more frequently in patients with ASD than in the general population (Burd *et al.* 2009; Freeman *et al.* 2000; Meier *et al.* 2015). As with most therapeutic algorithms pertaining to ASD, nonpharmacological interventions should be trialed first, before the initiation of medication. SSRIs have been used to target RRB in adults with ASD (Hollander *et al.* 2012; McDougle *et al.* 1996), especially since it has been postulated that anxiety may worsen some of these symptoms (Postorino *et al.* 2017), but these medications were generally no better than placebo in large-scale

studies, including fluoxetine (Herscu *et al.* 2020) and citalopram (King *et al.* 2009). Overall, the current literature does not support widespread use of SSRIs for targeting RRB symptoms in children and adolescents with ASD. Larger-scale studies are warranted, but they will require the use of novel measures with good psychometric properties so that researchers can capture all of the relevant RRB subdomains (see the appendix table at the end of this chapter). Tricyclic antidepressants such as clomipramine, which is beneficial for OCD, have also been examined in ASD (Pittenger and Bloch 2014), but results are also inconsistent (Hurwitz *et al.* 2012), and the associated side effects, including cardiotoxicity and severe anticholinergic effects, render this alternative less desirable. Medications that are approved for treating irritability and emotion dysregulation in ASD (e.g., risperidone and aripiprazole) have shown some potential for targeting RRB in ASD as well (McDougle *et al.* 2005b). Although their side-effect profiles limit their applications for many types of RRB, they have shown some efficacy and are approved for targeting very severe RRB-like self-injurious behaviors, which are extremely important therapeutic targets that appear in almost half (~42% on average) of autistic patients (Steenfeldt-Kristensen *et al.* 2020). Finally, with regard to tic disorders, atypical antipsychotics can be effective for managing these behaviors when first-line treatments such as a_2-agonists are not beneficial (Kurlan 2014; Shprecher and Kurlan 2009).

Emotion Dysregulation

Challenges with emotion regulation in individuals with ASD may manifest as severe irritability or aggression and may include significant maladaptive behaviors (McClintock *et al.* 2003; Tsakanikos *et al.* 2007), including self-injurious behaviors. Emotion dysregulation is also associated with significant distress for patients and stress for families, perhaps even more than that associated with the core defining features (Fitzpatrick *et al.* 2016; Lecavalier *et al.* 2006). The only FDA-and EMA-approved medications for ASD, risperidone at 0.3-3.5 mg daily and aripiprazole at 5-15 mg daily (see section "FDA-and EMA-Approved Treatments"), are used for improving emotion regulation to reduce severe irritability, aggression, and self-injurious behaviors (LeClerc and Easley 2015. A meta-analysis of the literature indicated that these medications are strongly effective for managing emotion regulation in children and adolescents with ASD (Fung *et al.* 2016), even more so than first-generation antipsychotics, which are not frequently prescribed because they are associated with more severe adverse effects, including EPS (Peluso *et al.* 2012). Risperidone and aripiprazole also appear to be superior--in terms of both efficacy and safety (Fung *et al.* 2016)--to the other antipsychotic agents that have been tested, including quetiapine, ziprasidone, and lurasidone (Fallah *et al.* 2019), which showed only minimal to marginal benefits in children and adolescents with ASD.

While antipsychotics have received most of the attention regarding emotion dysregulation in ASD, there is some limited evidence supporting the use of alternative medications. For instance, *N*-acetylcysteine (NAC), an over-the-counter dietary supplement that modulates glutamatergic signaling and increases antioxidative potential in the brain, exhibited moderate effects for reducing the severity of both irritability and stereotyped behaviors in a pilot trial of children with ASD (Hardan *et al.* 2012). NAC also further decreased irritability when used as an adjuvant to risperidone treatment (Ghanizadeh and Moghimi-Sarani 2013; Nikoo *et al.* 2015). Additional agents that exhibited some potential benefit in targeting emotion regulation in trials of autistic patients include atomoxetine (an SNRI), tianeptine (an opioid receptor

agonist), naltrexone (an opioid receptor antagonist), clonidine (an a_2-adrenergic agonist), methylphenidate (a dopamine and norepinephrine reuptake inhibitor), and valproate (an anticonvulsant that blocks some excitatory and increases some inhibitory effects). However, benefits shown by these other agents have been limited, have not yet been replicated, or have been inconsistent across the small-scale studies that have been completed to date. Aripiprazole and risperidone are the current first-line medications for reducing the severity of emotion dysregulation, irritability, aggression, and self-injurious behaviors in children and adolescents with ASD. These medications should be prescribed only for patients who have not responded to psychosocial interventions (e.g., applied behavior analysis-based treatments). Patients taking aripiprazole or risperidone will require regular monitoring for changes in weight, the development of EPS, and fluctuations in serum laboratory results.

Seizures and Epilepsy

The prevalence of seizure disorders in ASD is estimated to be very high, with some reports suggesting that approximately 10% of children and as many as 20%-40% of adolescents and adults with ASD have epilepsy (Amiet *et al.* 2008; Danielsson *et al.* 2005; Liu *et al.* 2022; Viscidi *et al.* 2013). These figures are notably higher than the 1%-2% prevalence observed in the general population (Frye *et al.* 2013). Seizures may also have an earlier onset in some children with ASD, be more resistant to treatment, and appear more frequently in autistic girls and individuals with intellectual developmental disorder, lower language skills, poorer adaptive functioning, or more severe core symptoms (Sansa *et al.* 2011). To date, there have been no RCTs of antiepileptics that specifically focused on epilepsy or seizures in autistic individuals. Currently, the treatment of these conditions in the context of ASD remains the same as in patients without ASD and is largely dependent on the type of seizure that the patient is experiencing. It has been suggested that patients who have epilepsy should first be given a trial on a broad-spectrum antiepileptic (Abou-Khalil 2008); however, no formal recommendations can be made, and treatment recommendations cannot be further refined for individuals with comorbid diagnoses of ASD and epilepsy because of the limitations of the current research.

Sleep Disturbances

Sleep disturbances are also very common in children with ASD, of whom as many as 80% have parent-reported sleep problems (Couturier *et al.* 2005; Polimeni *et al.* 2005). Imbalances in various neurotransmitter systems including melatonin, serotonin, and GABA have been hypothesized to underlie some sleep problems (Kotagal and Broomall 2012; Souders *et al.* 2017), with melatonin being the most commonly prescribed medication for sleep in patients with ASD (Relia and Ekambaram 2018). Most initial small RCTs of melatonin reported benefits for reducing time to sleep onset and increasing sleep duration compared with placebo (Garstang and Wallis 2006; Rossignol and Frye 2011; Wright *et al.* 2011), and a larger RCT ($N = 134$) corroborated these improvements and reported further benefits for reducing bedtime resistance and frequency of nighttime awakenings (Cortesi *et al.* 2012). When melatonin was taken in conjunction with cognitive-behavioral therapy, patients were noted to have even greater improvements in sleep continuity and efficiency. In children 2 years and older, melatonin should be started at 1 mg before bedtime ("Melatonin" 2021) and increased as tolerated. The dosage may be titrated up but should not exceed 10 mg/day. There are also several other alternative medications, such as clonidine, that have been studied in the context of sleep improvement in ASD (Huffman *et al.* 2011), but these medications have limited evidence of efficacy because of the small sample sizes that have been investigated to date (Ming *et al.* 2008; Rossi *et al.* 1999). Atypical antipsychotics including risperidone and olanzapine have also been used for sleep disturbances in some children, but these medications are not first line and are typically prescribed off label (Relia and Ekambaram 2018). The various metabolic and EPS associated with atypical antipsychotics further limit their use to refractory cases only.

Nutritional Deficiencies

Nutritional deficiencies, which are more common in children with ASD than in the general population, are largely associated with food aversions and sensory sensitivities, but there are inconsistent observations about the types and effects of these deficiencies. Despite individuals with ASD eating more restricted varieties of food (Ranjan and Nasser 2015), several investigations have reported no differences in calorie, carbohydrate, or fat intake (Emond *et al.* 2010; Lockner *et al.* 2008; Zimmer *et al.* 2012), and the findings on protein intake are inconsistent (Ranjan and Nasser 2015; Xia *et al.* 2010; Zimmer *et al.* 2012). Children with ASD are also commonly deficient in minerals such as calcium (Hyman *et al.* 2012; Lockner *et al.* 2008; Zimmer *et al.* 2012), iron (Cornish 2002; Herndon *et al.* 2009), and zinc (Cornish 2002; Hyman *et al.* 2012). Common vitamin deficiencies associated with ASD include vitamins A (Cornish 2002; Lockner *et al.* 2008), B_2 (Cornish 2002), B_9 (Al-Farsi *et al.* 2013; Xia *et al.* 2010), B_{12} (Al-Farsi *et al.* 2013; Cornish 2002), C (Evans *et al.* 2012; Xia *et al.* 2010), D (Bandini *et al.* 2010; Herndon *et al.* 2009), and E (Herndon *et al.* 2009; Lockner *et al.* 2008), which are also reflected in serum analysis (Ranjan and Nasser 2015). Although such deficits are common, correction of nutritional deficiencies is not typically associated with any changes in the core symptom domains, and there is not yet convincing evidence supporting nutritional therapy for most patients with ASD (Karhu *et al.* 2020). This absence of evidence also extends to omega-3 supplements, digestive enzymes, and most vitamin supplements (Sathe *et al.* 2017). In cases of severe or symptomatic nutritional deficiency, supplemental nutritional therapy is still warranted and should be considered by the clinical care team. It is important to consider that certain alternative nutritional therapies, such as gluten-free or casein-free diets, are commonly implemented for children with ASD, such that as many as 20% may have been tried on a gluten-free diet (Rubenstein *et al.* 2018). The evidence supporting such dietary approaches is very limited, and dietary restrictions could predispose some patients to deficiencies in essential vitamins, minerals, fiber, and carbohydrates (Mari-Bauset *et al.* 2014; Sathe *et al.* 2017). Thus, it is essential to provide adequate counseling on the benefits and risks of nutritional therapies to support shared decision-making with patients and their caregivers (Hebert 2014).

Novel Pharmacological Agents for the Core Symptoms of Autism Spectrum Disorder

Neuropeptides

Neuropeptides are small proteins (i.e., nanopeptides) that act primarily though G protein-coupled receptors to modulate synaptic transmission. Oxytocin and vasopressin are two such neuropeptides that regulate many important social behaviors in the mammalian brain, including reproduction, childbirth, and social bonding. Administration of oxytocin and vasopressin to humans has been associated with improved social communication, emotion recognition, eye contact, and other prosocial behaviors as well as changes in repetitive and compulsive behaviors (Meyer-Lindenberg *et al.* 2011). Therefore, it should come as no surprise that these particular neuropeptides have received considerable interest for targeting the core symptoms of ASD (Bartz and Hollander 2008), particularly oxytocin. Despite reports that single-dose and open-label intranasal administrations improved social cognition in neurotypical individuals (Guastella and MacLeod 2012) and reduced core symptom severity in individuals with ASD (Guastella and Hickie 2016), RCTs have been inconsistent, with some trials failing to replicate these initial findings (Anagnostou *et al.* 2012; Guastella *et al.* 2015; Yamasue *et al.* 2020). As with other investigational agents, the extreme neurobiological variability across autistic individuals, and individual differences in the neurobiology of the oxytocin system, probably contributed to some differences in treatment response (Kosaka *et al.* 2016; Parker *et al.* 2017; Yatawara *et al.* 2016). Consistent with this observation, a small RCT (N = 32) reported greater improvement in social abilities after 4 weeks of oxytocin compared with placebo, but only after controlling for baseline oxytocin levels, which also predicted treatment response (Parker *et al.* 2017). Unfortunately, a large multisite trial examining the safety and efficacy of oxytocin failed to replicate these preliminary findings on their primary outcome of reciprocal social behaviors (Sikich *et al.* 2021), and there is no strong evidence that supports oxytocin treatment for children and adolescents with ASD.

While investigations of oxytocin have reported disappointing results so far, interest in vasopressin and its role in modulating social abilities has also emerged, with recent studies examining the safety and efficacy of both vasopressin agonists and antagonists. In a double-blind, randomized, placebo-controlled study, daily intranasal administration of a vasopressin agonist treatment was examined in 30 children with ASD for 4 weeks. Compared with placebo, vasopressin was associated with greater improvement in social abilities and decreases in anxiety symptoms and repetitive behaviors (Parker *et al.* 2019). There is also limited evidence supporting the potential for vasopressin antagonists to target some core ASD symptoms. An initial investigation of the vasopressin V1a receptor antagonist balovaptan in adult men with ASD observed changes in secondary endpoints on the Vineland Adaptive Behavior Scale composite score, with some changes in socialization and communication (Bolognani *et al.* 2019), but follow-up studies failed to replicate these findings on the Vineland Adaptive Behavior Scale when it was used as the primary outcome measure (Hollander *et al.* 2022). Because of their potential to directly target the mechanisms that may underlie some of the core social symptoms of ASD, drugs that modulate both the oxytocin (NCT02985749, NCT03466671) and the vasopressin pathways (NCT03204786) are currently being tested in Phase II and III RCTs enrolling children and adults with ASD, including an RCT examining intranasal oxytocin in combination with psychosocial therapies (NCT02918864).

Neurosteroids

Neurosteroids and neuroactive steroids are endogenous molecules that are synthesized either directly from cholesterol in the central nervous system or from peripheral steroid precursors (Baulieu and Robel 1990; Paul and Purdy 1992). They are highly lipophilic and can modulate neuronal excitability in the brain via interactions with ligand-gated ion channels (e.g., GABA_A and *N*-methyl-D-aspartate receptors), alter gene expression through nuclear hormone receptors, and potentially play a critical role in the pathophysiology of some psychiatric disorders, especially neurodevelopmental disorders like ASD in which there are sex differences in the prevalence and clinical phenotype. Pregnenolone is of particular importance because it is the precursor to virtually all neurosteroids. Preliminary investigations have reported that salivary levels of pregnenolone may be elevated in some children with ASD (Majewska *et al.* 2014), whereas plasma levels of pregnenolone sulfate, a primary metabolite, may be reduced (Jansakova *et al.* 2020). Although the potential role of neurosteroids in the pathophysiology of ASD is not yet known, recent pilot studies have reported some promising preclinical and clinical results. Administration of ganaxolone, a synthetic analog of allopregnanolone, to a mouse model of ASD was associated with improved social and reduced repetitive behaviors (Kazdoba *et al.* 2016). The first open-label study of oral pregnenolone in adults with ASD also reported reduced irritability, lethargy, and sensory processing difficulties (Fung *et al.* 2014). The first RCT in adolescents with ASD also reported decreased irritability, stereotypy, and hyperactivity compared with placebo when used as an add-on to risperidone (Ayatollahi *et al.* 2020). There is currently only one active Phase II RCT of pregnenolone in adolescents and adults with ASD (NCT02627508), which will examine changes in irritability as the primary outcome measure.

Pregnenolone is also a negative allosteric modulator of the cannabinoid 1 (CB_1) receptor, which may mediate some of its effects on autism-related symptoms.

Cannabinoids

The endocannabinoid system has also been implicated in ASD, with reports from preclinical models suggesting that it is involved in the modulation of many of the cellular functions and molecular pathways that have been implicated in the disorder, including imbalanced excitation or inhibition, increased oxidative stress, mitochondrial dysfunction, and immune dysregulation (Zamberletti *et al.* 2017). Clinical studies support these preclinical models with reports of lower plasma (Karhson *et al.* 2018) and serum (Aran *et al.* 2019) levels of endocannabinoids in autistic children and adults. Furthermore, preclinical and clinical studies also suggest that agents targeting the endocannabinoid system may provide clinical benefits for patients with ASD. However, investigations into the potential use of medicinal cannabinoids (e.g., cannabidiol [CBD], cannabidivarin) for psychiatric disorders have been limited because of the effects of ethical and societal debates on local and federal regulations, especially regarding their use by children and adolescents. The first clinical trial of an orally administered cannabinoid to children, adolescents, and adults with ASD was only recently completed in Israel. The study authors reported that high-dose CBD and low-dose tetrahydrocannabinol (the main psychoactive compound) were generally well tolerated, with only mild adverse effects, such as somnolence and decreased appetite, but they did not find any treatment-related changes in the primary outcome measure of disruptive behaviors (Aran *et al.* 2021), which may have been related to the heterogeneous sample that was evaluated. Alternatively, they did report significant clinician-rated changes in externalizing behaviors as well as some secondary effects

on social communication. More recently, changes in local regulations and federal enforcement across the United States have allowed new research into the use of medicinal cannabinoids, and at least four clinical trials are being conducted to examine the safety, tolerability, and potential efficacy of various cannabinoid solutions for children and adolescents with ASD. One exploratory open-label study (NCT03900923) and three separate RCTs (NCT04517799, NCT04745026, and NCT04745026) are exploring whether CBD can be used to improve a wide range of core and comorbid symptoms. Thus, further guidance on the use medicinal cannabinoids for children with ASD should be available in the near future.

Beta-Adrenergic Antagonists

b-Adrenergic antagonists (a.k.a. beta-blockers) block the effects of epinephrine and norepinephrine in organs such as the heart and brain and are most commonly used for the treatment of cardiovascular diseases (e.g., hypertension, cardiac arrhythmia, myocardial infarction, and congestive heart failure), glaucoma, and migraine prophylaxis. In psychiatric disorders, b-blockers are commonly used off label in the management of aggression and anxiety, especially performance anxiety (Newman *et al.* 2013), and have received considerable attention in ASD for their potential to target core social symptoms and self-injurious behaviors (Sagar-Ouriaghli *et al.* 2018). Initial case studies indicated that high dosages of propranolol (> 300 mg/day on average; range 120-900 mg/day) may help with management of self-injurious, aggressive, and other challenging behaviors (London *et al.* 2020; Sagar-Ouriaghli *et al.* 2018), but no RCTs of propranolol have been completed to date that support this indication for patients with ASD. Propranolol has received increased attention because of several single-dose challenge studies in adolescents and adults with ASD that reported benefits in cognitive performance, including language processing, working memory (Beversdorf *et al.* 2011; Bodner *et al.* 2012), and social communication (Zamzow *et al.* 2016), that are associated with neurophysiological changes in the brain (Hegarty *et al.* 2017, 2019, 2020b; Narayanan *et al.* 2010). To date, there have been no published results from RCTs of propranolol used for targeting the core symptoms of ASD, but two are under way. These studies will examine target engagement of propranolol in the brain and will assess its efficacy for improving social communication in children with ASD (NCT02871349) and its potential efficacy for targeting irritability, aggression, and self-injurious behaviors in adolescents and adults with ASD (NCT04047355).

Drugs for Neurodegenerative Disorders

Memantine is an *N*-methyl-D-aspartate receptor antagonist that is commonly used to treat Alzheimer's disease, especially when acetylcholinesterase inhibitors are ineffective or contraindicated. Memantine can reduce the potential for excitotoxicity by inhibiting prolonged influx of calcium into the neuron while still allowing neurotransmission because of its low affinity and uncompetitive nature compared with glutamate. Based on this potential to reduce the adverse effects of excessive excitatory signaling in the brain, memantine has received some attention for the treatment of ASD. Early open-label investigations reported some improvements in core areas of social communication and self-stimulatory behaviors (Chez *et al.* 2007) as well as potential improvements in other domains such as memory, irritability, and hyperactivity (Owley *et al.* 2006). Much like other drug trials, results from the first RCTs of memantine for ASD also failed to replicate these early findings, with reports of no drug-related differences on the Social Responsiveness Scale (SRS [Constantino and Gruber 2005]), a questionnaire designed to identify the presence and severity of impairments in social communication in ASD (Aman *et al.* 2017). Subsequent trials then attempted to identify potential responders in an open-label trial before randomization in an RCT (Hardan *et al.* 2019). In the open-label study, 60% of the intention-to-treat sample of children with ASD (*N* = 868) were identified as responders because they exhibited at least a 10-point reduction in the SRS total raw score from baseline. Then 93% of these responders were enrolled in the randomized withdrawal trial, with 33% assigned to placebo, 33% to the full memantine dosage from the open-label study, and 34% to a reduced dosage ([?] 50% of the open-label dosage). Of those randomly assigned, 30% completed the study and approximately 66% discontinued due to loss of their therapeutic response (i.e., [?] 10-point increase in the SRS score from baseline). An approximately equal proportion of participants from each arm relapsed, and there were only negligible differences in terms of treatment response at the end of the trial (Hardan *et al.* 2019). At this time, the available evidence does not support the use of memantine for core symptoms of ASD, and there is only one current RCT that is targeting social deficits in children and adolescents with social impairments (NCT03553875), including ASD.

Nutritional Supplements

Children with ASD often have limited diets because of their selective eating patterns or alternative therapies that may be associated with nutritional deficiencies. Therefore, nutritional supplements are attractive treatment options because they are easily available over the counter, typically well tolerated with minimal side effects, and inexpensive compared with other forms of treatment. The most common supplements that have been investigated to date include vitamins A, C, B_6 and B_{12}, magnesium, and folate, but the available research indicates limited efficacy of these supplements for improving the core symptoms of ASD (Karhu *et al.* 2020). There are some novel applications of other readily available compounds that have exhibited potential efficacy in preliminary trials for ASD. For instance, NAC is a synthetic derivative of the endogenous amino acid L-cysteine that replenishes endogenous levels of glutathione, a primary antioxidant and glutamatergic modulator in the human body. NAC has received considerable attention in psychiatry for targeting a range of symptoms in multiple disorders (Deepmala *et al.* 2015), including ASD. At high dosages, NAC has exhibited some efficacy for treating irritability in autistic children as well as promising preliminary results for reducing the severity of some RRB symptoms (Hardan *et al.* 2012). A single-dose challenge study to examine target engagement of high dosages of NAC in the brains of children with ASD (NCT04278898) and an RCT to assess the potential efficacy of NAC for reducing core RRB severity (NCT05664789) are currently being conducted.

Another promising nutritional supplement for children with ASD is sulforaphane. Sulforaphane is an organosulfur compound that is derived from broccoli sprouts and like NAC has both antioxidative and anti-inflammatory effects in the central nervous system. In the first preliminary trial, sulforaphane reduced some aberrant behaviors, such as irritability and hyperactivity, as well as the severity of social impairments in adolescents and adults with ASD (Singh *et al.* 2014). However, these results were only

partially replicated in a subsequent pediatric study, such that changes in core social symptoms did not differ from those of patients taking placebo (Zimmerman *et al.* 2021). There is currently one other RCT under way to further investigate sulforaphane as a potential treatment for core ASD symptoms (NCT02677051).

Finally, several recent studies have also examined the potential for folinic acid to target language delay and improve communication skills in children with ASD. Preliminary findings from pilot RCTs of folinic acid derivatives (i.e., leucovorin) included improved language and communication scores (Frye *et al.* 2018; Renard *et al.* 2020) as well as reduced inappropriate speech and problem behaviors when used as an adjuvant treatment to risperidone (Batebi *et al.* 2021). These promising findings have facilitated the development of several larger RCTs that are currently examining the potential efficacy of folinic acid in children with ASD between the ages of 2.5 and 12 years who have language delay (NCT04060030, NCT04060017, NCT02839915).

Summary of Recommendations and Guidance

The optimal approach for treating autistic patients who are seeking mental health care services is to maintain a balance between psychosocial/behavioral interventions and medications. It is critical to reevaluate treatment regimens on a regular basis to determine whether specific medications or psychotherapies continue to be beneficial. This strategy will avoid excessive polypharmacy and eliminate therapies that are not benefiting the patient. In light of the limited evidence supporting the efficacy of available pharmacological agents in the treatment of core features of ASD, the focus of the psychiatric evaluation is to identify the existence of any DSM-5 diagnoses. This approach will allow the use of specific interventions to treat specific comorbid disorders. For example, making the diagnosis of major depressive disorder could support prescription of an antidepressant. However, the complex and atypical presentations of psychiatric symptoms in people with ASD, especially those with intellectual developmental disorders, make pinpointing particular comorbid disorders difficult or impossible. Therefore, targeting symptoms such as aggression and irritability with medications may be the only alternative approach, even though is not ideal. It may also be tempting to consider targeting different behaviors with more than one medication. For example, children with ASD commonly present with sleep disturbances, anxiety symptoms, and inattention, hyperactivity, and impulsivity. This constellation of symptoms probably requires different medications, but it is recommended that target symptoms be prioritized on the basis of either severity or patients' and parents' preferences to minimize the potential for more complex and severe adverse events, which may be more common in autistic patients.

By definition, individuals with ASD have difficulties with their expressive abilities, and this limitation may be even more pronounced in those with intellectual developmental disorders. Hence, assessing emergent side effects and monitoring treatment progress can be very challenging, and the clinician should request input from multiple sources in addition to the patient. Reporting on dry mouth or cognitive side effects, for instance, might not be possible for some patients. In these cases, behavioral dysregulation might be the manifestation of some adverse effects related to the prescribed medications. Determining whether benefits are being observed is also not straightforward at times, and it is often necessary to gather information from all involved parties, including parents or legal guardians, teachers, classroom aides, bus drivers, in-home therapists, group home staff, and day program supervisors. The collection of standardized measures and questionnaires is also critical to support a more comprehensive evaluation of the overall behaviors and symptom profiles and, more importantly, to allow a comparison over time and across settings and contexts. Multiple scales are available to help measure different symptom domains, and some of the most commonly used instruments are outlined in the appendix table.

Finally, once a medication is initiated, response rates can vary such that some individuals may respond dramatically, while others exhibit only a minimal response. This variability is not surprising considering the extreme neurobiological heterogeneity of ASD and involvement of many different neural networks and neurotransmitter systems. Therefore, rechallenging with the same medication 1 or 2 years later might lead to a different response or better tolerance because the targeted brain pathways are developing over time. The sensitivity of a neural network to one medication or lack of responsiveness to another might also change as the brain is maturing. For example, it is not surprising if a 7-year-old girl with ASD and ADHD is not able to tolerate 10 mg/day of methylphenidate, with emergent irritability and sleep disturbances, but is able to take a 20 mg/day extended-release formulation of the same compound at age 10 years with good response.

Future Directions and Advancement of Precision Medicine

Current Limitations

Behavioral therapy is typically the first-line treatment for patients with ASD, and pharmacological interventions are currently directed at the management of comorbid psychiatric and medical conditions. The lack of pharmacological interventions for the core symptoms of ASD is partially due to limitations of drug trials for this patient population. First and foremost, treatment response to even the most efficacious drug intervention is extremely variable across patients. The extreme phenotypic and neurobiological heterogeneity across ASD patients, changes in treatment response over different developmental periods, increased incidence of psychiatric and medical comorbidities, and limitations of the available outcome measures for assessing treatment-related changes have all hindered clinical trials for ASD to date. Innovative clinical trial designs will be necessary to account for and address these complicating and confounding factors and will be critical for advancing the development of new pharmacological treatments for patients with ASD who are seeking mental health care services.

Domain-Specific and Objective Outcome Measures

One of the most important aspects of clinical trial design is the selection of reliable and valid outcome measures that are sensitive to change. Outcome assessment tools used to measure changes in core ASD symptom severity have been extremely variable across clinical trials, as have their psychometric properties. Attempts have been made to identify the most appropriate outcome measures for trials targeting SCI and RRB (Anagnostou *et al.* 2015; Scahill *et al.* 2014), but there continue to be significant limitations in even the most frequently recommended approaches. The appendix table at the end of this chapter presents examples of traditional instruments that are commonly used for monitoring core symptom severity in autistic patients, including the SRS, 2nd Edition, for SCI (Constantino and Gruber 2012), the Restricted Behavior Scale for RRB (Lam and Aman 2007), and the Short Sensory Profile for sensory processing patterns (Tomchek and Dunn 2007). Recent investigations using big data applications for psychometric research in ASD have also begun to address some of the limitations of these previous measures by developing novel assessment tools for specific subdomains of the core symptom domains, such as the Stanford Social Dimensions Scale (Phillips *et al.* 2019) and the Dimensional Assessment of Repetitive Behaviors (Uljarevic *et al.* 2023).

Combination of Pharmacological and Psychosocial Interventions

Psychosocial and behaviorally based interventions are the first-line treatment for children with ASD, whether they are targeting core features or comorbid domains. However, much like with pharmacotherapies, treatment response to psychosocial and behavioral interventions is also extremely variable across autistic patients. Some of this variability in treatment response is probably related to individual differences in cognition and behavior, such as attention, emotion regulation, and externalizing or internalizing behaviors (Lerner *et al.* 2012). Thus, pharmacological agents that can improve one symptom domain in children and adolescents with ASD may also help optimize treatment response to behavioral or psychosocial interventions targeting other symptom domains. For instance, antipsychotic medications are associated with a faster response to intensive behavioral interventions targeting aggression (Frazier *et al.* 2010) and improving adaptive and social communication skills when used in combination with parent training to reduce maladaptive behaviors (Scahill *et al.* 2012). More importantly, RCTs are starting to assess the efficacy of combined pharmacological and psychosocial treatments, which may help optimize patient outcomes and advance the development of precision medicine for subgroups within the autism spectrum.

Biomarkers

Finally, there is mounting evidence that there are clinical and biological subgroups within the autism spectrum, for which optimal treatment approaches probably differ from mainstream recommendations. Clinical or phenotypic subgroups are those who share similar cognitive and behavioral symptom profiles. For instance, autistic individuals with significant cognitive challenges (e.g., IQ < 70), delayed language development with minimal spoken communication skills (e.g., nonverbal), high severity of certain types of RRB (e.g., specific rigidities), or high versus low motivation for social engagement and interaction may have more in common with each other than with the general ASD population and be more likely to respond to the same interventions. Similarly, biological and genetic subgroups who share similar neurobiological profiles may also be more likely to respond to certain interventions. For instance, autistic individuals with shared genetic architectures (e.g., fragile X), brain abnormalities (e.g., macrocephaly or cerebellar alterations), neurotransmitter imbalances (e.g., hyperserotonergia or excitation/inhibition imbalances), or neurophysiological alterations (e.g., seizures) may be more likely to respond to some treatments than to others. Genetics and more specifically pharmacogenomics, which examines the role of the genome in drug response, may also potentially aid in identifying subgroups within ASD. Biomedical scientists have begun to make progress in other areas of medicine (e.g., oncology), and there is great promise for psychiatry in general as well as for the field of ASD specifically. Although limited work focused on pharmacogenomics in ASD has been published, the available literature supports testing for two cytochrome P450 genes (*CYP2D6*, *CYP2C19*) before prescribing certain antidepressants and antipsychotics, testing for human leukocyte antigen genes (*HLA-A* and *HLA-B*) before using certain mood stabilizers, and screening for genes affecting the urea cycle (*OTC*, *CSP1*) before considering valproate when a urea cycle disorder is suspected (Bousman *et al.* 2021).

Conclusion

Despite the promising research described above, no clear progress has been made in developing new interventions for the core symptom domains of ASD and other developmental disorders or in identifying specific subgroups with distinct neurobiological underpinnings or common clinical features, including prognostic outcomes. Therefore, additional research is critical and must include the development of innovative and adaptive study designs, more sensitive assessment and measurement tools that incorporate big data science and artificial intelligence, and new patient stratification and surrogate outcome markers to advance clinical research for ASD. This innovative research will also aid in the identification of novel therapeutic agents for targeting specific core symptom domains such as insistence on sameness and low social motivation, as well as comorbid domains such as anxiety and depression. Ultimately, more objective assessment tools and the identification and study of subgroups within the autism spectrum should help reduce trial and error of interventions and should advance precision medicine for autistic patients who are seeking mental health care services.

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APPENDIX

Outcome Measures for Assessment of Core Symptom Domains in Autism Spectrum Disorder

APPENDIX: Details of outcome measures used for clinical monitoring and clinical trials for autism spectrum disorder

Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales

Acknowledgment. The authors would like to thank Katherine Paszek (Stanford University) for creating this table.

Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales
Global functioning					
Clinical Global Impression (CGI) (Busner and Targum 2007) * Clinician-administered summary interview that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.	Clinician	Any age	Varies with familiarity with patient	12	Severity of illness Global improvement Efficacy index
Social communication					
Social Responsiveness Scale, 2nd Edition (SRS-2) (Constantino and Gruber 2012) * Questionnaire that assesses the presence and severity of social impairments related to ASD. Can help distinguish between social impairment in ASD and social impairment that occurs in other disorders; can also be used to monitor symptoms across the life span.	Caregiver, Teacher, Self-report	Preschool (2.5-4.5 years), school age (4-18 years), adult (19+ years)	15-20	65	Social awareness Social motivation Social communication Social cognition Restricted, repetitive behaviors and interests
Social Communication Questionnaire (SCQ) (Rutter *et al.* 2003) * Questionnaire (lifetime & current forms) that assists with evaluation of communication skills	Caregiver	4+ years	< 10	40	Reciprocal social interaction Communication Repetitive behavior

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Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales
and social functioning in children who may or may not have ASD. Often used as a screener for ASD and requires caregivers to be familiar with the developmental history and current behavior of the individual.					
Stanford Social Dimensions Scale (SSDS) (Phillips *et al.* 2019) * Dimensional, quantitative parent-report questionnaire designed to capture key social processes and skills that, if impaired, can impede a person's ability to navigate the complexities of the social worlds. Can be used in both normative and clinical populations.	Caregiver	Any age	15-20	58-71	Social motivation Social affiliation Expressive social communication Social recognition Unusual approach
Brief Observation of Social Communication Change (BOSCC) (Grzadzinski *et al.* 2016) * Videotaped observation assessment of social communication behaviors in children with ASD. Sensitive to changes in social communication behavior and can be administered by minimally trained examiners and coded	Clinician	1-5 years	12	15	Social communication Restricted, repetitive behaviors

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Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales
quickly by nonexpert raters.					
Communication and Symbolic Behavior Scales (CSBS) (Wetherby *et al.* 2002) * Questionnaire/videotaped observation that assesses communication, social-affective functioning, and symbolic abilities in children to support early identification of those with (or at high risk of) social communication impairment.	Caregiver, Clinician	8-24 months	50-75	24	Social composite Speech composite Symbolic composite
Social Skills Improvement Scale (SSIS) (Gresham and Elliott 2008) * Questionnaire designed to assess individuals and small groups to evaluate social skills, problem behaviors, and academic competence. Because ratings can be collected from multiple informants, SSIS can provide a comprehensive assessment across multiple settings.	Caregiver, Teacher, Self-report	3-18 years	10-25	58-84	Communication Cooperation Assertion Responsibility Empathy Engagement Self-control
Restricted and repetitive behaviors					
Children's Yale-Brown Obsessive Compulsive Scale: Modified for Autism Spectrum Disorder (CYBOCS-	Caregiver	4-17 years	15-30 (varies with child's RRB)	70	Hoarding and ritualistic behavior Sensory and arranging behavior Sameness and self-injurious behavior

Acknowledgment. The authors would like to thank Katherine Paszek (Stanford University) for creating this table.

Domain/scale or measure	**Reporter**	**Age range**	**Administration time (min)**	**No. items**	**Subscales**
ASD) (Scahill *et al.* 2014) * Modified version of the CYBOCS semistructured interview specifically designed for rating severity of repetitive behaviors in children and adolescents with ASD and other development disorders. Parents/patients list the four most troublesome target behaviors based on time spent, interference, distress, resistance, and degree of control.					Stereotypy Restricted interests
Repetitive Behavior Scale-Revised (RBS-R) (Lam and Aman 2007) * Questionnaire used to capture the breadth of repetitive behavior in ASD. Caregiver is asked to refer to the previous month when completing the scale. Has been validated for use in young children with ASD.	Caregiver	6-17 years	15	43	Rituals/sameness Self-injurious behavior Stereotypical behavior Compulsive behavior Restricted interests
Dimensional Assessment of Repetitive Behaviors (DARB) (Uljarevic *et al.* 2023) * Questionnaire developed and validated following methods outlined by the National Institutes of Health Patient-Reported Outcome	Caregiver	3-18 years	25-30	99	Repetitive motor behaviors Insistence on sameness Restricted interests Unusual interests Self-injurious behaviors Sensory sensitivity Obsessions and compulsions Repetitive language

Acknowledgment. The authors would like to thank Katherine Paszek (Stanford University) for creating this table.

Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales
Measurement Information System (PROMIS) framework. The comprehensive set of items provides in-depth domain coverage and range to capture change for each of the RRB subdomains.					
Sensory processing					
Sensory Perceptions Quotient (SPQ) (Tavassoli *et al.* 2014) * Questionnaire providing a quantitative measurement of individual differences in basic sensory perception. Aids in differentiating between adults with and without ASD.	Self-report	Adults	8-10	35	Touch Hearing Vision Smell Taste
Short Sensory Profile (SSP) (McIntosh *et al.* 1999; Tomchek and Dunn 2007) * Brief questionnaire that assesses observable child behaviors. Enables differentiation between children with and without sensory processing challenges.	Caregiver	3-15 years	10-15	38	Sensory system scores: Auditory, Visual, Touch, Movement, Body position, Oral Behavior scores: Conduct, Social-emotional, Attentional Sensory pattern scores: Seeking, Avoiding, Sensitivity, Registration
Infant/Toddler Sensory Profile (Daniels and Dunn 2000) * Caregiver questionnaire used to evaluate sensory processing patterns in very young children. Helps provide an	Caregiver	Birth-36 months	10-15	24-54	Sensory processing: General, Auditory, Visual, Tactile, Vestibular, Oral Sensory quadrants: Low registration, Sensation seeking, Sensory sensitivity, Sensation avoiding, Low threshold

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Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales
understanding of how sensory processing affects the child's daily functioning.					
Child Sensory Profile-2 (CSP-2) (Dunn 2014) * Caregiver questionnaire supporting evaluation of sensory processing patterns in children across multiple contexts, including home, school, and community settings.	Caregiver	3-15 years	10-15	86	Sensory system scores: Auditory, Visual, Touch, Movement, Body position, Oral Behavior scores: Conduct, Social-emotional, Attentional Sensory pattern scores: Seeking, Avoiding, Sensitivity, Registration
Adolescent/Adult Sensory Profile (AASP) (Brown and Dunn 2002) * Self-report questionnaire that helps measure sensory processing patterns and their effects on daily functioning. Supports informed intervention planning.	Self-report	11-65+ years	10-15	60	Quadrant: Low registration, Sensation seeking, Sensory sensitivity, Sensation avoiding Sensory processing: Visual, Auditory, Touch, Taste/smell, Movement, General
Language					
Peabody Picture Vocabulary Test, 4th Edition (PPVT-4) (Dunn and Dunn 2007) * Clinician-administered direct assessment of receptive (hearing) vocabulary of children and adults. During administration, the examiner says a word, and the examinee responds by pointing to the picture that best represents the word's meaning.	Clinician	2.6-90+ years	10-15	228	Receptive vocabulary

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Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales
Preschool Language Scales, 5th Edition (PLS-5) (Zimmerman *et al.* 2011) * Clinician-administered direct assessment of developmental language that includes items ranging from evaluation of preverbal, interaction-based skills to emerging language and early literacy skills.	Clinician	Birth-7 years	45-60	Varies with child's ability	Auditory comprehension Expressive communication
Clinical Evaluation Language Fundamentals, 5th Edition (CELF-5) (Wiig *et al.* 2013) * Clinician-administered direct assessment supporting accurate diagnosis of language disorders in children and adolescents. Tasks test language abilities in addition to observation-and interaction-based tasks, allowing clinicians to identify strengths and weaknesses.	Clinician	5-21 years	35-45	Varies with child's age	Core language score Receptive language index Expressive language index Language content index Language structure index Language memory index
Adaptive functioning					
Vineland Adaptive Behavioral Scale, 3rd Edition (VABS-3) (Sparrow *et al.* 2017) * Interview/questionnaire that provides a norm-referenced measure of adaptive behaviors. Was developed to support diagnosis of intellectual and	Caregiver, Teacher	Birth-90 years	20-60	577	Communication Daily living skills Socialization Motor skills

Acknowledgment. The authors would like to thank Katherine Paszek (Stanford University) for creating this table.

Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales
developmental delays and disabilities.					
Adaptive Behavior Assessment Systems, 3rd Edition (ABAS-3) (Harrison and Oakland 2015) * Questionnaire providing a complete picture of adaptive skills across the life span. Targeted toward individuals with developmental delays, ASD, learning disabilities, intellectual disability, neuropsychological disorders, and sensory or physical impairments.	Caregiver	Birth-89 years	15-20	193-239	Conceptual Social Practical
Challenging behaviors					
Aberrant Behavior Checklist (ABC) (Aman *et al.* 1985) * Informant-rated questionnaire empirically derived by principal component analysis. Designed to be completed by any adult who knows the client well, such as a parent, teacher, workshop supervisor, case worker, or informants in other roles.	Caregiver, Clinician, Community members	5 years-adult	10-15	58	Irritability Social withdrawal Stereotypic behavior Hyperactivity/noncompliance Inappropriate speech
Child Behavior Checklist (CBCL) (Achenbach and Rescorla 2001) * Questionnaire used across multiple contexts	Caregiver, Teacher, Self-report	1.5-18 years	10-20	113	Delinquent behavior Aggressive behavior Withdrawn Somatic complaints

Acknowledgment. The authors would like to thank Katherine Paszek (Stanford University) for creating this table.

Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales
to screen for emotional, behavioral, and social problems in children and adolescents. Often used as a screening assessment and for referral for services. Has been studied cross-culturally and translated into multiple languages.					Anxious/depressed Social problems Thought problems Attention problems OR Externalizing problems Internalizing problems Total problems
Nisonger Child Behavior Rating Form (NCBRF) (Tasse *et al.* 1996) * Informant-rated questionnaire for assessing behavior of children and adolescents. Completed by a person who knows the child well. Informant is asked to assess child's behavior during the past month.	Caregiver, Teacher	3-16 years	15	76	Social competence Problem behaviors
Anxiety					
Spence Children's Anxiety Scale (SCAS) (Spence 1998) * Self-report questionnaire used to assess anxiety symptoms in children and adolescents. A parent-report version is also available. Higher scores indicate greater anxiety.	Self-report, Caregiver	8-15 years	5-10	38-44	Generalized anxiety Panic/agoraphobia Social phobia Separation anxiety Obsessive compulsive disorder Physical injury fears
Multidimensional Anxiety Scale for Children, 2nd Edition (MASC-2) (Wei *et al.* 2014) * Questionnaire that assesses the presence of	Caregiver, Self-report	8-19 years	15	50	Anxiety scales Obsessions and compulsions Physical symptoms Harm avoidance

Acknowledgment. The authors would like to thank Katherine Paszek (Stanford University) for creating this table.

Domain/scale or measure	Reporter	Age range	Administration time (min)	No. items	Subscales
symptoms related to anxiety disorders in youth. Distinguishes between important anxiety symptoms and dimensions that broadband measures do not capture.					
Parent Rated Anxiety Scale-Autism Spectrum Disorder (PRAS-ASD) (Scahill *et al.* 2019) * Questionnaire that assesses the severity of anxiety in youths with ASD and can support evaluation of change in treatment.	Caregiver	5-17 years	5	25	Anxiety

Acknowledgment. The authors would like to thank Katherine Paszek (Stanford University) for creating this table.

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CHAPTER 67

Treatment of Psychiatric Emergencies

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Psychiatric emergencies occur in every situation and in every setting, and the diagnosis and management of these emergencies is a fundamental skill of every practicing psychiatrist. Although often managed in specialized crisis stabilization units, psychiatric emergencies occur in other locations, such as general medical/surgical units, outpatient clinics, general emergency departments (EDs), and other, nonclinical areas. The effective practice of emergency psychiatry requires a broad range of knowledge and clinical skills, including general and consultative psychiatry, behavioral neurology, psychopharmacology, individual and family psychotherapy, geriatric psychiatry, and addiction medicine. In addition, a basic knowledge of forensic and legal issues is essential in all settings.

The increasing prevalence of psychiatric emergencies as reflected in general hospital ED visits is striking. There were 420,000 ED visits per year for attempted suicide and self-injurious behaviors between 1993 and 2008 (Larkin *et al.* 2005). Between 2007 and 2016, ED visits related to mental health complaints rose from 6.6% to 10.9% (Theriault *et al.* 2020). This trend of steady increases in psychiatric emergency presentations to general hospital EDs has continued, despite the ongoing impact of COVID-19 (Holland *et al.* 2021).

Patients with emergent behavioral and psychiatric syndromes are often unable or unwilling to provide accurate historical details; therefore, the clinician must rely on collateral sources of information, including friends, family, and previous treatment providers. One consequence of this process of data collection is that absolute patient confidentiality, the standard of care in other clinical settings, is more tenuous. The Health Insurance Portability and Accountability Act (HIPAA) regulates all disclosures of protected health information (PHI) by health care providers. In 2014, the U.S. Department of Health and Human Services issued guidance on the implementation of HIPAA in the setting of psychiatric emergencies (U.S. Department of Health and Human Services 2014). In the context of a psychiatric emergency, the need to acquire critical information supersedes the individual's absolute right to privacy. The guiding principle is the determination of the clinician, based on professional judgment, that disclosure of certain PHI would be in the best interests of the patient in that emergent situation. Disclosures to family, friends, and other care providers can be made if the patient does not object when informed of the proposed disclosure, or if, in the professional judgment of the clinician, the patient does not have capacity based on their mental status (examples being psychosis, substance intoxication, or unresponsive states). In emergent situations, resources such as medical records, friends, and relatives may provide critical data for diagnosis and treatment. There is no prohibition in HIPAA against a clinician listening to information provided by family, friends, and other care providers or reading outside clinical records. In the emergency situation, accurate diagnosis and treatment is critical, and although any health disclosures should be minimized, the focus is on safety. There are other circumstances in which there is a mandated breach of confidentiality, including situations in which a patient is at risk of harming self or others (e.g., knowledge of potential child or elder abuse). HIPAA does not prevent these mandatory disclosures to protect the safety of the patient or others. Specific disclosure and third-party contact requirements vary by jurisdiction and should be reviewed by psychiatrists who are subject to them.

As the numbers of psychiatric emergency cases continue to increase, and both a shortage of psychiatrists and increasing safety concerns during a pandemic impact delivery, telemedicine has become increasingly important in the practice of emergency psychiatry. Telepsychiatry was described in the literature in 1973 (Dwyer 1973) and primarily existed to provide care in urgent cases to remote areas. Telepsychiatry use has peaked during the COVID pandemic, increasing from less than 1% of visits to (in places heavily impacted by COVID) up to 80% of visits (FAIR Health 2020). Telemedicine has become increasingly utilized by specialty services, including emergency psychiatry (Reinhardt *et al.* 2019). Providers who engage in telepsychiatry must be aware of regional, state, national, and board level regulations that surround telepsychiatry, including but not limited to information security, insurance restrictions, and prescribing concerns.

Telepsychiatry is best utilized when it includes voice (or ideally voice and video), as this is seemingly superior to text-only exchanges (Galea *et al.* 2020). When the emergency permits, it is critical to acquire and document the patient's consent for the use of a telemedical device. Because there will always be potential connectivity or technical issues on either end of the remote visit, ideally the provider should test connectivity and video quality before the emergency presents itself. Given the potential for disruption, a provider should spend as much time as possible reviewing relevant documentation and laboratory findings before the visit is initiated. Although the nature of the emergency may preclude this, ideally patients should be asked directly if they feel comfortable with the process or if there are any off-screen issues that would prevent them from maintaining confidentiality of their health information. Providers should work to develop and maintain a therapeutic alliance, which is more challenging in remote interactions (Flint and Kotwal 2020). Performing a full neurological or physical exam is difficult (Benziger *et al.* 2021) but possible to approximate, and providers will need to work to gather as much collateral information as possible from available staff and families.

Clearly, development of a well-trained workforce of clinicians to deal with this rising tide of psychiatric emergencies is an urgent national imperative. The Accreditation Council for Graduate Medical Education (ACGME) does specify training requirements for emergency psychiatry for all psychiatric residents, which must be conducted in an organized, supervised psychiatric emergency service. Acknowledging the increasing importance of this education, the ACGME requirements exclude outpatient or on-call experiences from counting toward this experience. Efforts should continue to be made through the American Association of Directors of Psychiatric Residency Training (AADPRT) and other organizations to ensure that all psychiatry residents receive adequate, high-quality training in psychiatric emergencies. But given that in a large proportion of psychiatric emergency cases individuals present to general emergency rooms, it is clear that training in diagnosing and managing psychiatric emergencies should be provided to professionals other than psychiatrists, from physicians in emergency medicine residencies through nurses and other practitioners.

Nonpharmacological Psychiatric Emergencies

Situations that require emergent psychiatric intervention, but not psychopharmacological treatment, include evaluation of need for hospitalization, assessment of suicide or homicide risk, determination of ability to care for self, and requirements to notify third parties in order to ensure the safety of the patient or others (Table 67-1). Emergency psychiatrists must attempt to make predictions about patients' future behavior and work to take appropriate preemptive action to prevent negative outcomes. All states have civil commitment laws that allow for the involuntary hospitalization of persons who by virtue of a mental illness may be considered an imminent risk to themselves or others. Typically, these laws allow for commitments of 48-72 hours in secure receiving facilities. Involuntary hospitalization beyond this holding period for observation and stabilization generally involves judicial review.

TABLE 67-1. Psychiatric emergencies that do not require pharmacological intervention

Emergency	Intervention
Suicidal state	Risk assessment
	Decision to admit
Homicidal state	Evaluation for psychiatric disorder
	Risk assessment
	Decision to admit
	Notification to others if indicated
Child, elder, or spouse abuse	Notification of law enforcement and other agencies
	Referral to safe shelters
Grave disability (inability to care for self)	Medical evaluation
	Attempt to gather collateral information
	Decision to admit

Need for Hospitalization

Decisions to hospitalize a psychiatric patient are dependent on many factors but are always based on the welfare of the patient. There should be clear, definable treatment objectives for hospitalization, and the facility in which the patient is to be admitted should be capable of meeting those needs. Other factors that can contribute to the decision to hospitalize a patient include availability of psychiatric hospital beds and admission authorization by third-party payers (Simon 1998). Thus, the clinician must balance the availability of resources with the needs of individual patients.

Once the decision is made to hospitalize a patient, every effort should be made to have this occur on a voluntary basis. This is the first step in establishing therapeutic rapport with patients. The indiscriminate use of involuntary commitment can set up the perception of an adversarial relationship between patients and treatment providers (Olofsson and Jacobsson 2001). Avoiding experiences that elicit the perception of being "locked up" is one way of facilitating the long-term care engagement of the mentally ill patient.

Suicidal State

Suicide is the twelfth leading cause of death in the United States, with 45,979 suicide deaths in 2020, which translates into a population rate of around 14 deaths per 100,000 per year (Centers for Disease Control and Prevention 2023). The total age-adjusted suicide rate in the United States increased 35.2%, from 10.5 per 100,000 in 1999 to 14.2 per 100,000 in 2018, before slightly declining to 13.9 per 100,000 in 2019, and remained stable in 2020 (National Institute of Mental Health 2021). The increasing rate of suicide is indicative of the lack of impact of any specific psychiatric treatments on the suicide rate. Several studies have failed to find any association between the availability of psychiatric treatment resources and the suicide rate (Garlow *et al.* 2002; Lewis *et al.* 1994).

There is no evidence that predicting suicide can be accomplished with any degree of sensitivity or specificity (Kessler *et al.* 2020), and attempting to do so can provoke significant anxiety in the clinician (Pokorny 1983, 1993). This is relevant because almost half of adults who die by suicide have been seen by a provider within the past month, and almost half have visited an ED within the past year (Ahmedani *et al.* 2014; Luoma *et al.* 2002). Risk of suicide should be viewed in the context of these limitations. The relationship between suicidal ideation, attempted suicide, and completed suicide is complex and inconclusive (Moscicki 1997).

Suicide risk is estimated by assessing both acute and chronic risk factors (Table 67-2), which include patient characteristics, nature of suicidal behavior, availability of a high-lethality means, and level of and access to psychosocial support systems (e.g., family, friends, community) (Hall *et al.* 1999; Simon and Gutheil 2002). Acquiring reliable and accurate past and collateral history is essential. Acute risk factors are most predictive of emergent suicidality and should carry the most weight in the decision to hospitalize a patient (Busch *et al.* 2003).

TABLE 67-2. Common acute and chronic risk factors for suicide

Acute	Chronic
Previous suicide attempts	Gender (male : female = 4:1)
Escalating anxiety/panic attacks	Age (18-24 years; > 65 years)
Access to highly lethal means	American Indian/white
Hopelessness	Sexual minority
Substance intoxication	Access to highly lethal means
Mood-congruent nihilistic delusions	Family history of suicide
Psychic turmoil	History of mental illness
Recent discharge from a psychiatric hospital	Previous suicide attempts
Global insomnia	History of substance use disorders
	Marital status
	Childhood adversity

Generating a comprehensive suicide risk assessment involves organizing and balancing risk with protective factors. Clear documentation of these risk and protective factors, steps taken toward intervention, and associated clinical reasoning is essential. A basic statement describing competency should also be included. In the case of a patient chronically at risk for suicide, clearly documenting this pattern and obtaining a second opinion to corroborate the treatment plan and objectives may be beneficial.

Acute Risk Factors

A history of attempted suicide is the strongest single predictive factor for risk of completed suicide (Bostwick *et al.* 2016). Other acute risk factors include increasing anxiety and frank panic attacks, psychic turmoil, global insomnia, mood-congruent nihilistic delusions, profound hopelessness, and recent discharge from a psychiatric hospital (Busch *et al.* 2003; Deisenhammer *et al.* 2007; Fawcett 1992; Fawcett *et al.* 1990).

Current intoxication is another acute risk factor, as patients with a history of alcohol and drug use have a 10-14 times greater risk of completed suicide (Wilcox *et al.* 2004). Almost all substances of abuse are associated with an increase in the risk of suicide. The suicide hazard ratio is 1.35 for cocaine use, 2.10 for psychostimulant use, 3.83 for benzodiazepine use, 3.89 for cannabis use, and 11.36 for sedative use (Bohnert *et al.* 2017). Recent alcohol consumption plays a role in 25%-50% of all suicides (Cornelius *et al.* 1998).

Previous suicide attempts are known precursors for completed suicide; thus, nonlethal suicide attempts are acute risk factors (Deisenhammer *et al.* 2007; Isometsa and Lonnqvist 1998; Tejedor *et al.* 1999). Consideration should be given to the actual lethality of the attempt; the patient's perception of that lethality; efforts made to conceal the attempt; calls for help; contacts with friends or family during the attempt; and use of a firearm. Access to firearms must always be determined in suicide assessment--in the United States, firearms were used in over half of completed suicides (Centers for Disease Control and Prevention 2023).

Chronic Risk Factors

Males complete suicide three to four times more often than females, but females demonstrate a higher number of suicide attempts. Historically, males tend to choose more lethal and violent means of suicide than females. This may be changing. Among males, firearms remain the most commonly used method of suicide. Firearm-related suicide has increased in females and represented the leading means of completed suicide in 2020 (Centers for Disease Control and Prevention 2023). From 2000 to 2020, male suicide rates were consistently highest in those ages 75 and older. Female suicide rates between ages 45 and 64 were the highest during this time frame.

Rates of suicide are higher for American Indians/Alaska Natives and whites than for any other racial group. These suicide rates for specific racial groups change with the age and gender of the individual. In one study, African American males constituted the largest group, numerically and statistically, of teenage suicide victims but accounted for only 26% of victims from all age groups. In this same dataset, African American females accounted for only 3% of all suicides, with only one occurring in an individual older than 45 years (Garlow *et al.* 2005).

Approximately 90%-95% of suicide victims have a major psychiatric illness, of which approximately half have a mood disorder (Angst *et al.* 2002; Fawcett 1992; Harris and Barraclough 1997). Among individuals with bipolar disorder, males are at higher risk for suicide, especially those at an earlier phase of the illness, those who are currently in a depressed state, and those with comorbid substance abuse (Simpson and Jamison 1999). Patients with alcohol or other substance use disorders have higher rates of completed suicide than the national average, with alcoholic patients having a suicide rate that is twice the national average (Fowler *et al.* 1986). For individuals with alcohol use disorder, comorbid depression and recent interpersonal loss increase risk (Murphy and Wetzel 1990; Murphy *et al.* 1992). A family history of suicide increases suicide risk independent of a family history of mental illness (Qin *et al.* 2002, 2003). Sexual minorities are at an increased risk of suicide (Salway *et al.* 2019), as are adults who experienced childhood abuse (Zatti *et al.* 2017).

Patients with borderline personality disorder often express ongoing suicidal ideation; as a result, suicidality becomes embedded in their sense of self (Soloff *et al.* 1994). This can manifest as repeated acts of self-injurious behavior, such as cutting and sublethal overdoses. These patients can be very difficult to manage and can put a great deal of strain on the emergency medical and mental health delivery system. A consistently applied treatment plan, restrained responses on the part of clinical staff (minimizing countertransference behaviors), and use of secure 24-hour observation areas can be particularly useful in managing these patients. The goal is to allow patients to deescalate so that they can be discharged back into their ongoing outpatient treatment regimens (Maltsberger and Buie 1974).

Protective Factors

When a suicide risk assessment is being formulated, it is critical to note protective factors in addition to the presence or absence of acute and chronic risk factors. Protective factors against suicide include an expression of responsibility toward family, fear of social disapproval, moral objections to suicide, greater coping skills, and greater fear of suicide (Malone *et al.* 2000). Social connectivity also serves a protective role for depressed patients, as first described by Emile Durkheim (1951). Having close familial relationships, being in a stable marital or other partnered relationship, living with another person (family or friend), and having dependent children are all protective factors (Kleiman and Liu 2013). Belonging to certain cultural groups, such as a community of faith, and having moral objections to suicide are associated with lower rates of suicide (Dervic *et al.* 2004, 2006).

Management of Suicidal Patients

Ensuring safety is the first and most important step in managing a potentially suicidal patient. This can best be accomplished through admission to a secure patient observation area. If no such facility is available, close observation by a trained staff member is another option. Staff assigned to monitor patients should be given specific instructions regarding their role and responsibilities.

The decision to hospitalize a potentially suicidal patient should consider both acute and chronic risk factors; specific treatment needs of the patient; availability of any other treatment options, including partial hospitalization, day treatment, and crisis group home settings; and the social support network of the patient. Patients who are intoxicated and expressing suicidal ideation should be allowed to sober up before receiving a more definitive assessment. No-harm contracts between patients and clinicians are not useful in making treatment decisions with suicidal patients (Kroll 2000; Simon 1999). Focusing on the acute behavioral state of the patient (anxiety, agitation, and insomnia), the presence of chronic risk factors, and access to high-lethality means (firearms) is much more relevant to making the decision to hospitalize the patient.

Patients who are not hospitalized require close follow-up, ideally including an identified treatment provider and instructions for the patient and family members on what to do in case of symptom worsening. Recommendations for management of acutely suicidal outpatients have been operationalized into an approach called Safety Planning Intervention (SPI). SPI is specifically designed to be deployed in ED settings for patients with suicidal ideation who are not hospitalized. A trained staff member assists the patient in developing a written document that includes warning signs, coping mechanisms, and sources of support and other treatment resources (Stanley and Brown 2012). Individuals with access to high-lethality means should be advised to remove these items from the home. Firearms and medications lethal in overdose should be neither in the home nor readily accessible. Family members and friends may be consulted to assist with the removal of these items from the patient's possession (Mann *et al.* 2005).

Psychotherapy has shown benefit in the management of suicidal patients, with reduced mortality in patients who engaged with a therapist (Erlangsen *et al.* 2015). In one seminal report on the use of cognitive-behavioral therapy (CBT) with suicidal patients initially assessed in a general ED, patients who received a 10-session CBT intervention were much less likely to make a second suicide attempt within the 18-month follow-up period compared with those who did not receive this intervention (Brown *et al.* 2005). The patients who received CBT also had greater improvements in depression symptom severity and lower levels of hopelessness than those in the control group.

Although management of emergent suicide risk has historically not been considered to warrant acute pharmacological interventions, ongoing trials suggest that the

dissociative anesthetic agent ketamine may have specific therapeutic benefit in suicidal patients (Price and Mathew 2015). Single doses of subanesthetic ketamine (0.5 mg/kg body weight) have been shown to rapidly relieve symptoms of depression and suicidal ideation (Wilkinson *et al.* 2018). The antisuicide response appears to occur regardless of the impact on severity of mood symptoms, suggesting a specific antisuicide action of ketamine (Ballard *et al.* 2014). It remains unclear as of this writing whether ketamine can be useful in the management of unipolar depression or in longer-term treatment. Clearly, additional research is needed to fully determine the utility, if any, of this intervention in general clinical practice.

Homicidal State

Establishment of a psychiatric diagnosis is the first step in developing a management plan for a patient expressing homicidal ideation. Suicide most often occurs in the context of a mental illness, but with regard to homicide and assault, people with severe mental illness are significantly more likely to be the victim of violence than the perpetrator. Psychotic disorders are associated with an increased risk of violence, but this behavior is more closely correlated with substance abuse (Fazel *et al.* 2009).

Expressions of anger, hostility, rage, and violent intent occur in many interpersonal situations and conflicts in which the perpetrator does not have a psychiatric disorder. In these cases, once a determination has been made that the individual is not psychotic or delusional or expressing homicidal ideation due to some other psychiatric disorder, appropriate interventions are in the domain of law enforcement, not psychiatry.

If a patient who is expressing homicidal ideation is not admitted to a psychiatric facility, the clinician must give very careful consideration to the need to notify the intended victim and law enforcement agencies based on the principles set forth in *Tarasoff v. Regents of the University of California* (1976) (Simon 1998; Walcott *et al.* 2001). This case established a precedent for mental health workers to breach confidentiality to notify an intended victim and law enforcement agencies if they are aware of a patient's plan to harm that individual. Adoption of the principles set forth in the *Tarasoff* ruling varies by state but must be considered.

Predicting which individuals may act on homicidal ideation is very difficult (Fazel *et al.* 2009; Resnick and Scott 2000). Factors that contribute to this assessment are the specificity of the plan, identity of the victim, access to high-lethality means (firearms), capacity of the patient to persist in the plan, and proximity of the perpetrator to the intended victim (Borum and Reddy 2001). Even with a careful history, assessment, and appropriate intervention, preventing an adverse outcome may not be possible.

Child, Elder, or Spouse Abuse

Vulnerable individuals--children, elderly persons, or those with developmental disabilities and/or special needs--may present with psychiatric emergencies resulting from abuse and neglect. Responses to abuse and neglect may take the form of behavioral disturbances, self-injurious behavior, or failure to thrive and diminished self-care. The initial response from providers should be a careful and comprehensive evaluation and data gathering. When abuse and/or neglect is suspected or confirmed, involvement of social or legal services is an appropriate step. Depending on the locality and rules defining mandatory reporting by providers, notification of third parties may be required (see section below). Although care requirements in such cases will be determined by the underlying condition of the individual and the consequences of the abuse or neglect, interventions could involve medical treatment, general restorative measures (e.g., nutrition, physical therapy), and/or mobilization of social resources for needs such as housing and other care.

Notification of Third Parties in Cases of Abuse/Neglect or Intent to Harm

The principles set forth by the *Tarasoff* ruling in California encourage clinicians to act in the best interests of the intended victim, with notification of the intended victim and law enforcement agencies in the case of expressed homicidal ideation. This places a unique burden on psychiatrists--to predict future behavior of a patient and to assume responsibility for the welfare of another person with whom the psychiatrist does not have a therapeutic relationship.

Another circumstance that requires breach of patient confidentiality is notification of authorities in cases of suspected child abuse and/or neglect. All states have statutes that require clinicians of all disciplines to notify the appropriate agency in the case of suspected child abuse. Many states also have laws for reporting elder abuse and abuse of other vulnerable individuals. Some states have requirements to report abuse or illness based on profession.

Grave Disability and Inability to Care for Self

Another situation for which involuntary commitment laws exist is when a patient by virtue of a mental illness is unable to care for themselves. The nature of these commitment laws will vary by location; for example, some states also include "as a result of substance abuse disorders" under this heading, whereas others do not (Hall and Appelbaum 2002). It must be considered whether the patient cannot provide adequately for basic needs, shelter, food, and medical attention because of a mental illness. A common example of this situation is a patient with a psychotic disorder who is living on the streets, without regular or adequate nutrition, and neglecting their ongoing medical conditions. This situation is not the same as that in which a person is homeless because of some other occurrence or circumstance, because homelessness does not in itself constitute grave disability. Another common situation that falls under this heading is a patient with dementia or other profound cognitive impairments who has wandered away from their caregivers. In these cases, there is evolving literature surrounding "dispositional capacity" assessments. These evaluations should reflect the patient's ability to understand their circumstances, their ability to care for themselves, and the availability of others who can help meet their needs (Bourgeois *et al.* 2017).

Psychiatric Emergencies Requiring Minimal or Adjunctive Pharmacological Intervention

Psychiatric emergencies requiring minimal or adjunctive pharmacological intervention occur in many different situations, although many share a common thread of developing in response to some discrete, identifiable stressor (Table 67-3). The practice of crisis intervention psychiatry involves identifying the root cause or stressor of the presenting syndrome and developing a focused treatment plan. The principal therapeutic goals are to alleviate short-term distress, rapidly return the patient to their previous level of functioning, and prevent the development of a more serious long-term syndrome. The judicious use of psychopharmacological agents, in concert with psychotherapeutic, psychosocial, and family system interventions, can be particularly effective in these emergencies.

TABLE 67-3. Psychiatric emergencies requiring minimal or adjunctive pharmacological intervention

Emergency	Intervention
Adjustment disorder or acute grief	Diagnostic/psychosocial assessment
	Psychotherapy
	Social and family system interventions
	Short course of sedative-hypnotic
	Short course of benzodiazepine
	Selective serotonin reuptake inhibitor
Rape, assault, or trauma	Medical evaluation and treatment
	Law enforcement notification
	Psychotherapy
	Short course of sedative-hypnotic
	Short course of benzodiazepine
	Insult-specific psychotherapy:

Emergency	Intervention
	Rape counseling
	Spousal abuse counseling
	Violence victim counseling
Borderline personality disorder	Controlled environment/deescalation
	Psychotherapy (e.g., dialectical behavior therapy)
	Low-dosage antipsychotics
Panic disorder	Medical evaluation
	Short course of benzodiazepine
	Outpatient referral

Adjustment Disorders

Adjustment disorders are defined as the development of emotional or behavioral symptoms in response to an identifiable stressor occurring within 3 months of the onset of the stressor (American Psychiatric Association 2013). Common clinical manifestations of adjustment disorders encountered in psychiatric emergency settings involve a mixture of anxiety, depressive, and neurovegetative symptoms in response to some external stressor or crisis. The potential stressors are myriad, including death of a family member or friend, job loss, diagnosis of a serious medical condition, divorce and other disturbances of family function, and financial hardship. The response to the stressor is out of proportion to the severity of the stressor and results in significant impairment in functioning.

The principal interventions for adjustment disorders are psychotherapeutic, educational, and psychosocial. Most crises have a natural time course and resolution. Feelings of distress in response to many of these insults are innate and expected. Psychoeducational interventions are aimed at helping the patient realize that the syndrome is a self-limited and understandable response to the stressor. Often, patients with adjustment disorders have a sleep disturbance, so the short-term use of a soporific (diphenhydramine 25-50 mg, hydroxyzine 25 mg, trazodone 50-100 mg, or mirtazapine 7.5-15.0 mg) or a sedative-hypnotic (zolpidem 5-10 mg, zaleplon 5-10 mg, eszopiclone 2-3 mg, or ramelteon 8 mg) could be considered to assist in reestablishing a normal sleep-wake cycle. In general, benzodiazepine use should be avoided, because at this time there is no evidence that the early use of these agents prevents the eventual development of more serious disorders such as PTSD (Gelpin *et al.* 1996; Guina *et al.* 2015).

Acute Trauma

Patients who have been exposed to a catastrophic stressor or an acute psychological trauma are at risk for developing acute stress disorder or PTSD (Foa *et al.* 1989). The definition of a traumatic event includes direct personal experience of an event that involves actual or threatened death, injury, or threat to one's physical integrity or witnessing such an event or learning about such an event happening to a family member or close associate. Most people who experience such traumas do not go on to develop any psychiatric disorder, but a significant minority, up to 30%, will develop PTSD.

Behavioral indicators of risk of developing PTSD include heightened levels of arousal and coping via disengagement after a traumatic event (Mellman *et al.* 2001). Personalization of the traumatic event, especially thoughts that one might die, is another risk factor. The typical time course for posttraumatic reactions to resolve is on the order of 4 weeks. During this time, it is extremely common for all trauma victims to experience some of the symptoms of PTSD. One of the main early therapeutic goals should be to educate patients about this time course and to encourage them to return to treatment if these symptoms persist past 4 weeks or become particularly debilitating. Referral to trauma-specific psychotherapies (e.g., rape crisis or violent crime survivor groups) can be helpful to victims of these specific insults, as can cognitive processing therapy, CBT, and eye movement desensitization and reprocessing.

The use of benzodiazepines is controversial in the context of acute trauma. Although these medications may be useful in decreasing overall levels of anxiety, current evidence indicates these medications are ineffective for both the treatment and the prevention of PTSD. These medications may impair the benefit of therapy, and overall, the risk seems to outweigh the benefit (Guina *et al.* 2015). If the decision is made to use these medications, long-half-life agents, such as clonazepam and diazepam, minimize the risk of withdrawal or rebound anxiety (Davidson 2004).

Conditions That Require Medical Evaluation

With any acute change in mental status or sudden-onset change in behavior in a previously well individual, medical causes must be considered first, before it is assumed that the symptoms are a manifestation of a previously undiagnosed psychiatric disorder (Frame and Kercher 1991; Hall *et al.* 1978, 1981). This is especially true when the syndrome occurs outside of the usual age-based window of vulnerability. For example, new-onset psychotic symptoms in a patient older than 40 years or mania in a patient older than 50 years should be considered due to a medical condition until proven otherwise.

Panic Disorder

A patient presenting with new-onset dyspnea, tachycardia, diaphoresis, chest pain, and light-headedness should receive a thorough medical evaluation before being assigned a diagnosis of panic disorder. Many different conditions can present with some or all of these symptoms, including unstable angina and myocardial infarction, hypoglycemia, anemia, pulmonary embolism, asthma, obstructive pulmonary disease, gastroesophageal reflux disease, irritable bowel disease, hyperparathyroidism, hyperthyroidism, pheochromocytoma, Huntington's disease, Parkinson's disease, seizure disorder, and autoimmune disorders, such as systemic lupus erythematosus (Roy-Byrne *et al.* 2006). Only after these medical conditions have been ruled out should a diagnosis of panic disorder be entertained. Current FDA-approved medications for panic disorder include clonazepam and alprazolam (benzodiazepines), fluoxetine, sertraline and paroxetine (selective serotonin reuptake inhibitors [SSRIs]), and venlafaxine (a serotonin-norepinephrine reuptake inhibitor). SSRIs tend to be utilized as first-line treatments because of their general tolerability, lack of potential for dependence/misuse, and good safety profile (Katon 2006).

Dissociative Episodes

Amnestic symptoms and acute states of confusion should always be considered secondary to a medical or neurological condition until proven otherwise. Amnestic symptoms are common after head injury, during cerebrovascular accidents and transient ischemic accidents, in postictal states, with brain tumors, in intentional and unintentional intoxications, and in many other medical conditions. Another important diagnostic consideration is delirium resulting from any number of medical or metabolic causes. Establishing the correct diagnosis in this type of patient is facilitated by extended observation, with repeated assessments. This allows for detection of the fluctuating levels of consciousness and awareness common in delirium and of the temporal evolution of the amnestic symptoms due to other causes. Unobtrusive observation of these patients also allows for assessment of purposeful, deliberate, and organized behaviors, which are observed in patients with psychogenic or factitious amnestic conditions but often are not seen in individuals with medical or neurological conditions.

Catatonia

Catatonia is a syndrome characterized by the presence of at least three of the following symptoms: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypy, agitation, grimacing, echolalia, and echopraxia (Fink and Taylor 2006; Taylor and Fink 2003). Catatonia can occur in psychiatric and nonpsychiatric conditions and can be diagnosed in roughly 10% of psychiatric patients in acute inpatient services and ED settings (Fink and Taylor 2006). If a patient has not had previous documented episodes of catatonia in conjunction with a known psychiatric disorder, a medical cause should be sought vigorously. Episodes of catatonic behavior can occur in a variety of neurological and medical conditions, including

metabolic encephalopathies, viral encephalitis, cerebrovascular accidents, epileptic episodes, hypercalcemia, and adverse medication (e.g., antipsychotic) or drug (e.g., phencyclidine [PCP]) side effects. These conditions should be ruled out before a psychiatric diagnosis is made. Although no established standard of care exists for the treatment of catatonia, the patient should be initially assessed for hydration status, deep vein thrombosis risk, and pressure ulcers. First-line treatment for catatonia is a benzodiazepine or electroconvulsive therapy (Fink 2001; Rosebush *et al.* 1990).

Mania or Psychosis

New-onset mania or psychosis should always be approached as being potentially caused by a medical condition. The clinical context will guide the urgency of the medical evaluation. New-onset psychotic symptoms in a 40-year-old and new-onset mania in a 50-year-old should prompt an urgent medical evaluation. Such symptoms appearing in an adolescent or a young adult should still be evaluated medically, although not with the same urgency as in the older adult. These symptoms can be caused by brain tumors, cerebrovascular accidents, autoimmune disorders, multiple sclerosis, and hyperthyroidism. Many medications, including exogenously administered steroids and stimulants, as well as illicit drugs, can provoke manic and psychotic symptoms. Therefore, a thorough physical examination and a urine drug screen are essential components of the diagnostic workup.

Functional Neurological Symptom Disorder (Conversion Disorder)

Functional neurological symptom disorder (conversion disorder) is a diagnosis of exclusion. Accordingly, new-onset neurological symptoms, including nonepileptic seizures, nonanatomical movement disorders, paresthesia, paresis, and amnestic syndromes, should be thoroughly evaluated before being attributed to a psychogenic cause. Management of functional neurological symptoms includes a complete medical assessment and reassurance that the symptoms will resolve with time. Long-term management involves both physical rehabilitation and treatment of the underlying psychological conflict or distress. Family therapy can be a useful tool, given that family dynamics are often an essential part of the psychosomatic response to stress (Hurwitz 2004).

Psychiatric Emergencies That Usually Require Pharmacological Intervention

Management of severe behavioral emergencies typically require psychopharmacological intervention prior to definitive diagnosis (Table 67-4). Many psychiatric patients will have episodes of disorganized, disinhibited, agitated, aggressive, or violent behavior. These behavioral states can occur in individuals who are psychotic, manic, or intoxicated as well as in those who have neurological symptoms associated with traumatic brain injury, dementia, or delirium. Patients who are experiencing severe medication side effects also require pharmacological intervention, as do patients with substance use disorders in a withdrawal state.

TABLE 67-4. Psychiatric emergencies that usually require pharmacological intervention

Emergency	Intervention
Agitated, assaultive, aggressive, or violent behavior	
Etiology unknown	Calm, controlled, and adequate staff
	Seclusion or stimulus minimization

Emergency	Intervention
	Physical restraint
Primary psychotic or mood disorder	Medication:
	Lorazepam
	Haloperidol
	Second-generation antipsychotic
	Ketamine
Substance intoxication	Calm, controlled, and adequate staff
	Seclusion, restraint, and stimulus minimization
	Identify intoxicating agent
	Medication:
	Lorazepam
	Haloperidol
	Second-generation antipsychotic
	Ketamine
Delirium	Determine diagnosis
	Treat underlying cause
	Minimize medications
	If needed, IV or IM haloperidol or second-generation antipsychotic
Dementia	Diagnose underlying medical causes (e.g., urinary tract infection)
	Calm, controlled, and adequate staff
	Seclusion or stimulus minimization
	Reassurance and frequent orientation

Emergency	Intervention
	Low-dose antipsychotics
Substance withdrawal states	
Ethanol or sedative-hypnotic withdrawal	Benzodiazepine to stabilize withdrawal symptoms Controlled taper Referral to chemical dependency treatment
Alcohol withdrawal delirium	Supportive measures Medical intensive care unit Benzodiazepine taper
Opioid withdrawal	Symptomatic relief of physical symptoms Clonidine Antiemetics (promethazine or ondansetron) Loperamide Ibuprofen Methocarbamol Hydroxyzine
Medication side effects	
Antipsychotic-induced dystonia	Acute: Diphenhydramine 25-50 mg IV Maintenance: Diphenhydramine 25-100 mg once daily or

Emergency	**Intervention**
	Benztropine 0.5-4 mg once daily or
	Trihexyphenidyl 2-10 mg daily
Antipsychotic-induced akathisia	Discontinue or reduce antipsychotic
	Propranolol 10 mg two to three times a day
	Benzodiazepine
Neuroleptic malignant syndrome	Discontinue antipsychotic
	Immediate stabilization and medical intensive care:
	Cooling
	Hydration
	Anticoagulation if needed
	Dantrolene
	Benzodiazepine
	Electroconvulsive therapy
Anticholinergic delirium	Discontinue anticholinergic agent
	Use supportive measures
Hypertensive crisis	Manage blood pressure and use supportive measures
Serotonin syndrome	Immediate stabilization and medical intensive care
	Discontinue serotonergic agent
	Benzodiazepine
	Supportive measures
Priapism	

Emergency	**Intervention**
	Discontinue medications Urgent urology consult if no resolution
Selective serotonin reuptake inhibitor discontinuation syndrome	Reassurance and restart medications

Assaultive, Aggressive, or Violent Behavior

Assaultive, aggressive, and violent behaviors can have many different etiologies, including psychotic or delusional ideation secondary to a primary psychotic or mood disorder, intoxication, acute states of confusion associated with dementia and delirium, rage attacks in patients with personality disorders, and deliberate, volitional acts by antisocial individuals. The most important chronic risk factor for predicting violent behavior is a history of such behavior. Acute risk factors include over-or undercontrolled behavior. The former refers to an individual with decreased psychomotor activity, tension, anger, and paranoia, whereas the latter refers to a person who is agitated, intrusive, and verbally provocative. Intoxication is an independent acute risk factor that can potentiate violent behaviors in patients with many different diagnoses.

A well-trained staff of an adequate number in an appropriately designed facility is the best strategy for preventing violent episodes. Staff members who are trained to respond in a calm, deliberate, and nonthreatening manner help to establish an atmosphere of order and control. Preventing a violent act from occurring is preferable to responding to a violent act after it has occurred. It is better to have a patient take a medication voluntarily and orally before his or her behavior has escalated than to be required to involuntarily medicate the patient after a crisis has occurred. Research has suggested that clinicians may overutilize intramuscular injections because they are easy to administer (Damsa *et al.* 2006).

There are several pharmacological options in the acute management of the agitated patient. Available oral agents include benzodiazepines and antipsychotics. Lorazepam in 2-mg doses given every 45-60 minutes will sedate most patients by the second dose. Other alternatives are 15-20 mg of olanzapine, 4-6 mg of risperidone, or 5 mg of haloperidol in a single oral dose. If a patient with a known diagnosis of schizophrenia or bipolar disorder is experiencing a psychotic or manic decompensation, a second-generation (atypical) antipsychotic should be used. If the diagnosis is not known or is unclear, then lorazepam is a better choice, especially as acute intoxication with some agents--for example, anticholinergics such as diphenhydramine--may be worsened by the addition of second-generation antipsychotics. Patients should be monitored for an increased risk of respiratory depression and extrapyramidal side effects.

New alternatives to the established pill or tablet formulations of second-generation antipsychotics are available and have demonstrated positive results in comparative studies. Risperidal M-Tab, Zyprexa Zydis, and Abilify Discmelt are rapidly

dissolving forms of their parent agents. Risperidone is also available in an oral concentrate solution. These formulations exhibit benefit over the traditional pill formulation for patients who "cheek" medications (i.e., store the administered pill in their cheek and subsequently dispose of it rather than swallowing it) (Allen *et al.* 2001, 2005). The FDA has approved an inhaled form (marketed under the name Adasuve) of loxapine, a first-generation antipsychotic with second-generation properties (Alexza Pharmaceuticals, Inc. 2016). This route of administration may have a more rapid onset of action than other formulations; however, the overall clinical utility and safety of this agent have yet to be determined.

Involuntary administration of psychotropic medications is permitted in behavioral emergencies, although wide variations exist in the legal definitions and rules regarding the practice of administering involuntary medication. Clinicians should be well informed about the local definitions and regulations regarding involuntary administration of psychotropic medication. Accurate and timely documentation of the need for restraint and involuntary medication administration is essential. Response to the medication and observation for potential medical sequelae such as autonomic instability should also be documented.

Currently, several medications are suitable and commonly used for intravenous or intramuscular administration in behavioral emergencies: the benzodiazepines lorazepam and diazepam; the first-generation antipsychotic haloperidol; and the second-generation antipsychotics olanzapine, ziprasidone, and aripiprazole. Lorazepam is the most useful and should be the mainstay for controlling behavioral emergencies (Battaglia *et al.* 1997; Foster *et al.* 1997; Salzman *et al.* 1991). Lorazepam is rapidly absorbed from intramuscular injections, has a rapid onset of action and a short half-life, and is anxiolytic as well as sedating. Patients who are being combative generally are experiencing high levels of fear or anxiety, so the anxiolytic properties of lorazepam are an additional advantage. Absorption of intramuscular diazepam can be erratic; therefore, this medication is not particularly useful. Haloperidol should be reserved for patients who are clearly psychotic, with the expectation that they will be receiving long-term treatment with an antipsychotic agent.

In a behavioral emergency, a sufficiently large dose should be given with the first injection to ensure rapid onset of sedation and to minimize the need for a second or third injection. Lorazepam should be administered in a 2-mg dose that can be repeated at 45 minutes if the initial dose is insufficient. Very rarely will any additional injections be required after a second 2-mg dose of lorazepam. The initial haloperidol injection should be 2.5-5.0 mg and should not be repeated for at least 2 hours. Enough time must be given for the medication to be absorbed and for maximal sedation to occur. To prevent dystonia, 1 mg of benztropine should be included with intramuscular haloperidol, and haloperidol doses should not exceed 10 mg in 24 hours. Alternatively, 25 mg of diphenhydramine may be added to prevent dystonia while providing additional sedation. The combination of lorazepam and haloperidol in a ratio of 2 mg of lorazepam to 5 mg of haloperidol is often used to provide adequate sedation and anxiolysis while treating the underlying psychosis.

The injectable second-generation antipsychotics should be reserved for patients who will be given an oral second-generation agent after the immediate emergency has resolved. Intramuscular ziprasidone has been studied in patients with schizophrenia who were psychotic and agitated and is currently indicated for the treatment of this condition (Daniel *et al.* 2001; Lesem *et al.* 2001). In these clinical trials, patients received an initial injection of 10 mg, followed by injections of 5-20 mg every 4-6 hours, for a maximum dose of 80 mg in 24 hours. As defined in the package insert for intramuscular ziprasidone (Pfizer, Inc. 2022), the recommended dose is 10 mg or 20mg administered as required, up to a maximum of 40 mg/day. Doses of 10 mg may be given every 2 hours; doses of 20 mg may be given every 4 hours. The maximum recommended intramuscular dose over 24 hours is 40 mg. Intramuscular ziprasidone appears to have a low incidence of extrapyramidal side effects compared with intramuscular haloperidol (Brook *et al.* 2000). Results from one naturalistic study suggest that the use of intramuscular ziprasidone may reduce time in restraints for agitated patients compared with treatment with a first-generation agent (Preval *et al.* 2005).

Injectable olanzapine has been studied for use in agitated patients with schizophrenia, bipolar mania, or dementia (Breier *et al.* 2002; Meehan *et al.* 2001, 2002; Wright *et al.* 2001). In the schizophrenia trials, patients received up to three individual injections of 2.5-10.0 mg in 24 hours, with the higher doses producing more significant and sustained reduction of agitation. In the bipolar trials, patients received up to three injections of 5 or 10 mg of olanzapine in 24 hours, with significant reduction in agitated behaviors. In the dementia trial, agitated patients received up to three olanzapine injections of 2.5 or 5 mg in 24 hours, with significant reduction in agitation. A review of the literature by Tulloch and Zed (2004) concluded that injectable olanzapine was superior to placebo in all study populations and was superior to intramuscular lorazepam in individuals with bipolar disorder. However, this review further concluded that injectable olanzapine did not differ significantly from intramuscular haloperidol or lorazepam in the management of agitation associated with schizophrenia/schizoaffective disorder or dementia. It is relevant to note that olanzapine is FDA approved for the treatment of schizophrenia and bipolar mania, but not for management of agitation associated with dementia.

Injectable aripiprazole is approved for the treatment of agitation in patients with schizophrenia and bipolar mania. Efficacy studies found that injectable aripiprazole at a dose of 9.75 mg was superior to placebo and comparable to injectable olanzapine. Injectable aripiprazole demonstrated tolerability and symptom reduction without oversedation (Tran-Johnson *et al.* 2007).

Other agents utilized in emergent situations include midazolam and ketamine. Midazolam is a rapidly sedating benzodiazepine and can be given intramuscularly at a typical dose of 2.5 to 3 mg. It has a rapid onset but a short duration, and patients will potentially require additional medications. Midazolam is a potent sedating agent and should not be given without airway support being immediately available (Knott *et al.* 2006). Ketamine has demonstrated efficacy in rapid agitation control at a low dose (5 mg/kg) via intramuscular injection. Again, there must be means available to obtain immediate airway control (Barbic *et al.* 2021).

Primary Psychotic or Mood Disorder

Schizophrenia

Atypical (second-generation) antipsychotics represent the current standard of care for the treatment of acute agitation in patients with schizophrenia (American Psychiatric Association 2004). With proven efficacy and improved tolerability in comparison with haloperidol, these agents represent the first-line treatment in the agitated psychotic patient (Aleman and Kahn 2001; Currier and Trenton 2002; Yildiz *et al.* 2003). The optimal intervention in a patient with schizophrenia who is experiencing an acute exacerbation is to rapidly initiate treatment with a second-generation antipsychotic. In this regard, risperidone and olanzapine are the most useful agents, because both can be initiated at a high therapeutic dose (15-20 mg for olanzapine; 4-6 mg for risperidone) and can be given in multiple oral doses (two or three doses) over a period of 24 hours.

In a patient who is too disorganized or combative to take medication orally, intramuscular administration is the only viable route. Currently, the most commonly available injectable antipsychotics are chlorpromazine, haloperidol, ziprasidone, olanzapine, and aripiprazole. In a patient who is psychotic and agitated, coadministration of a benzodiazepine during the first few days of treatment can be particularly effective in controlling behavior while the antipsychotic response develops. Studies suggest that this combination may reduce the total antipsychotic dosage required and potentially result in fewer adverse antipsychotic effects (Salzman *et al.* 1991; Yildiz *et al.* 2003). One caveat to this choice of treatment is the increased risk of sedation and cardiorespiratory depression associated with the combined use of intramuscular olanzapine and intramuscular lorazepam, which led to a black box warning in the prescribing information provided by Eli Lilly, the manufacturer of olanzapine (Lilly USA 2021).

Bipolar Disorder

The goal of managing acutely manic individuals is to rapidly establish a long-term definitive treatment regimen, which means initiating a mood-stabilizing agent such as lithium (10-20 mg/kg) or valproic acid (20-30 mg/kg) as soon as possible. Prior to initiating either of these two agents, a serum pregnancy test should be obtained and documented as negative, since both agents are teratogenic. Both lithium and valproic acid require time to reach a therapeutic blood level and may take up to 14 days to become fully effective. Until steady state is established, behavioral control can be achieved with oral or intramuscular lorazepam on an as-needed basis or with a second-generation antipsychotic such as olanzapine, risperidone, ziprasidone, asenapine, quetiapine or aripiprazole, all of which are FDA approved for the treatment of acute bipolar mania. Olanzapine, risperidone, and quetiapine have the advantage of being sedating, which can be useful in an emergency room setting. A review of the literature indicated that intramuscular olanzapine was superior to lorazepam monotherapy in the treatment of agitated manic patients (Tulloch and Zed 2004). If the long-term plan does not include an antipsychotic, lorazepam or another benzodiazepine should be used for short-term behavioral control. If, however, the plan is to use both a mood stabilizer and an antipsychotic for long-term management, an antipsychotic should be substituted for the benzodiazepine.

Substance Intoxication

Violent and combative behavior by intoxicated patients is a very common occurrence in psychiatric and medical emergency departments. Alcohol, cocaine, PCP, methamphetamines, g-hydroxybutyrate (GHB), and hallucinogens and "designer" drugs (modified cathinones such as bath salts and Flakka) can lead to violent behavior. Recent research in a large urban psychiatric emergency room suggests that use of designer drugs may be a larger problem than was previously appreciated. In this

analysis, standard urine drug screening systems missed a significant number of cases of drug ingestion. Use of a more sensitive enzyme-linked immunosorbent assay (ELISA) and gas chromatography-mass spectrometry (GC-MS) system identified patients who had ingested opiates and amphetamines that were not detected by the standard screening test. This more sensitive detection system also identified a number of patients who had used designer drugs such as cathinone derivatives and tryptamines, which are not detectable with standard screening systems (Reidy *et al.* 2014).

Ethanol intoxication is a very common cause of violent behavior. The appropriate interventions are physical restraint and sedation with a benzodiazepine or haloperidol if the agitation is significant, to allow the patient to become sober. Once a patient's blood alcohol level is below the legal limit for intoxication, a more definitive evaluation can be undertaken, focusing on presence of any underlying psychiatric diagnosis or other treatment needs.

Prolonged cocaine use can lead to development of both mood and psychotic syndromes. Transient paranoid states are very common in cocaine users, as are frank delusions and hallucinations. Agitated paranoid states accompanying cocaine intoxication can lead to significant violent behavior. Interventions include seclusion and restraint, use of intramuscular lorazepam, and use of an antipsychotic if the patient is frankly psychotic. When the patient is no longer intoxicated, the presence of underlying psychopathology can be assessed.

PCP intoxication can be particularly provocative of agitated, combative, and violent behavior. Fortunately (or unfortunately), PCP use tends to occur in localized geographical regions. In areas where PCP use is common, intoxicated individuals are common in emergency facilities. PCP intoxication can present with frank psychotic symptoms, agitation, disorientation, and disorganized behavior. Violent outbursts can be sudden, unprovoked, and unexpected. Patients in the throes of PCP intoxication can be insensitive to pain, and so may be prone to continued agitation even if seriously injured. Adequate numbers of well-trained staff are essential when dealing with patients who have been using PCP. Restraint rooms should be dark and quiet to minimize stimulation. Intramuscular lorazepam should be used to sedate the patient. The half-life of PCP is 20 hours, so these behavioral states can persist for several days before fully resolving.

Methamphetamines (and designer drugs such as bath salts and Flakka, which are amphetamine-like) and GHB can cause agitated, disorganized, and violent behavior. Methamphetamine can have behavioral consequences very similar to those of cocaine. Because of the long half-life of methamphetamine compared with cocaine, this drug can be particularly provocative of frank paranoid and psychotic symptoms. These patients can have psychotic, paranoid, agitated, and violent presentations.

Presenting symptoms of methamphetamine intoxication often include agitation, hallucinations, suicidal ideation, and chest pain (Derlet *et al.* 1989). Distinguishing stimulant intoxication from other clinical conditions can be challenging, given the symptom overlap. Generally, stimulant-induced psychosis tends to be distinguishable from primary psychotic disorders by the absence of a thought disorder and a prominence of visual hallucinations (Harris and Batki 2000). However, given the potential for comorbidity, a positive drug screen does not completely discount the diagnosis of a mood or psychotic disorder. Treatment should focus on maintaining the patient's safety while awaiting the drug's metabolism and dissipation from the patient's system.

Delirium

Patients with delirium can become disorganized, agitated, and combative. Delirium is defined as a state of disturbance in attention, awareness, and cognition, during which the symptoms occur rapidly and fluctuate with time. Delirium is usually due to one or several general medical conditions or to substance intoxication or withdrawal (American Psychiatric Association 2013). Delirium is a medical emergency and carries a very high burden of morbidity and mortality. The definitive treatment of delirium requires diagnosing the underlying cause and taking corrective action. No medications are currently approved for the management of delirium. Interventions aimed at controlling behavior include restraints, environmental modification including frequent reorientation of the patient, and if needed the use of intravenous haloperidol. Behavioral control is essential so that the patient does not further injure him-or herself or interfere with treatment and to protect staff and other patients. The first intravenous dose of haloperidol should be 2.5 mg. If the individual is still agitated after 2 hours, the dose should be increased to 5 mg. This dose can be repeated in another 2 hours if the person continues to be agitated. Haloperidol therapy has been associated with clinically significant QT prolongation. Once the patient is stabilized, a routine antipsychotic regimen should be initiated, dividing the total daily dosage into two or four doses. The antipsychotic can be decreased and discontinued as the delirium clears. Benzodiazepines are contraindicated in cases of delirium.

Dementia

Patients with dementia can become agitated, combative, or psychotic for many different reasons. The most common cause for these symptoms is a delirium superimposed on the dementia. Definitive diagnosis and treatment of the disorder causing the delirium are essential to achieving adequate long-term resolution. Patients with dementia who are not delirious can become agitated as a result of confusion or psychosis inherent in the neurodegenerative pathology. In these cases, the best interventions are nonpharmacological and include environmental modification, behavior modification, and supportive measures. Aggressive behavior in patients with dementia can be treated pharmacologically, in the short term with low-dose antipsychotics and in the long term with low-dose antipsychotics, the anticonvulsants carbamazepine and valproic acid, the b-blocker propranolol, the SSRI antidepressants, or the anxiolytic drug buspirone. As is true in all geriatric prescribing, low doses and slow titration schedules define the appropriate course. Second-generation antipsychotics are not approved for the treatment of dementia-related psychosis, and the prescribing information carries a black box warning regarding an increased risk of death from cerebrovascular events (e.g., sudden cardiac arrest) and infections (e.g., pneumonia) in elderly patients who are treated with these agents (Schneider *et al.* 2005).

Substance Withdrawal States

Alcohol and Sedative-Hypnotics

Alcohol or sedative-hypnotic withdrawal can result in a frank delirium that is life-threatening (Marco and Kelen 1990; Olmedo and Hoffman 2000). The acute signs of early alcohol, sedative-hypnotic, and benzodiazepine withdrawal are similar and can include autonomic instability, tremulousness, diaphoresis, and gastrointestinal disturbances. Autonomic signs of withdrawal can include tachycardia, hypertension, and hyperthermia. Treatment of this withdrawal state is best accomplished with symptom-triggered (based on vital signs and/or Clinical Institute Withdrawal Assessment [CIWA] scores) administration of a long-half-life benzodiazepine. Use of long-half-life agents such as diazepam or chlordiazepoxide prevents peaks and troughs in blood levels. Lorazepam and oxazepam have relatively less hepatic sequelae. During the first 72 hours, vital signs and/or CIWA scores should be obtained at 2-to 4-hour intervals and additional benzodiazepine given if vital signs are still elevated. This approach has been shown to reduce total time and medication exposure in the detoxification phase. It is important to consider concomitant medications, given that b-blockers prescribed for a general medical condition may mask the autonomic signs of withdrawal.

Alcohol withdrawal delirium (delirium tremens) is a life-threatening medical condition (Erwin *et al.* 1998). This syndrome has a very high mortality rate--up to 35% in untreated patients and as high as 5%-15% in optimally treated patients. The delirium usually develops 48-72 hours after discontinuation of alcohol or sedative-hypnotics, peaks around day 4, and can persist for weeks. The symptoms include autonomic instability, fever, disorientation, perceptual disturbances and hallucinations, agitation, and confusion. Patients with delirium tremens should be treated in a medical intensive care unit. These patients typically require physical restraint and vigorous supportive measures. Intravenous haloperidol can be used to control agitation and psychosis. High doses of benzodiazepines have also been used in this situation to manage agitated behavior.

Wernicke-Korsakoff syndrome is another consequence of long-term alcohol use. Wernicke encephalopathy is the symptom complex of ophthalmoplegia, ataxia, and an acute state of confusion. Wernicke-Korsakoff syndrome is diagnosed if persistent learning and memory deficits are also present. Alcoholic individuals should receive three daily 100-mg doses of thiamine via the intramuscular route from the day of presentation, followed by three daily oral doses to prevent development of this syndrome. Patients should receive the first intramuscular dose before oral or intravenous administration of a carbohydrate load in order to prevent rapid thiamine depletion and emergent development of Wernicke-Korsakoff syndrome. Patients should also be given folic acid and magnesium replacement supplementation.

Opiates

Opiate withdrawal can be exceedingly uncomfortable for the patient but, unlike alcohol and sedative-hypnotic withdrawal, is generally not life-threatening. Accordingly, the goal of opiate withdrawal treatment is relief of pain and suffering. Symptoms of opiate withdrawal include dysphoria, anxiety, irritability, craving, mydriasis, piloerection, diaphoresis, nausea, vomiting, diarrhea, rhinorrhea, lacrimation, insomnia, fever, and hypertension. Onset of this syndrome depends on the half-life of the drug used and with heroin is usually 6-8 hours after the last use. The syndrome can last 2-5 days, depending on the individual patient. Clonidine in doses of

0.1-0.3 mg every 3 hours, up to 0.8 mg/day, can be given to suppress signs of opiate withdrawal (Ahmadi-Abhari *et al.* 2001; Akhondzadeh *et al.* 2000; Charney *et al.* 1981; Gossop 1988). A major side effect of this regimen is hypotension, so the regimen must be carried out in a medically supervised setting. Clonidine should be avoided in individuals who are dependent on both opiates and alcohol or a sedative-hypnotic; clonidine may mask the autonomic signs of ethanol withdrawal without preventing the emergence of delirium tremens. Other agents commonly utilized for symptomatic opiate withdrawal include promethazine or ondansetron, loperamide, ibuprofen, methocarbamol, and hydroxyzine.

Psychotropic Medication Side Effects

Antipsychotics

Several adverse events can occur in patients taking antipsychotics. Dystonic reactions are characterized by extreme muscle contraction and rigidity in a patient with stable vital signs and a clear sensorium. These occur most frequently with high-potency first-generation antipsychotics (Moleman *et al.* 1982; Schillevoort *et al.* 2001). Young males are particularly susceptible to dystonic reactions. Most dystonic reactions are extremely uncomfortable and frightening to the patient. Treatment of these reactions is typically 1-2 mg of benztropine via the oral or intramuscular route. An alternative is diphenhydramine in doses of 25-50 mg via the oral or intramuscular route. Dystonias that include the eyes, the so-called oculogyric crises, are particularly frightening, as are dystonias that cause laryngeal spasms, which can compromise the airway. These reactions should be treated with 50 mg of intramuscular diphenhydramine, which provides rapid relief. Maintenance treatment with 1-2 mg of benztropine twice a day or 25-50 mg of diphenhydramine twice a day should be initiated after the acute reaction has resolved (Keepers *et al.* 1983).

Akathisia is a syndrome characterized by internal restlessness, often perceived as the need to be in motion. This leads to increased psychomotor activity, including pacing, rocking, leg tapping and bouncing, and moving frequently between sitting and standing. The patient may complain of feeling anxious or irritable, or of having the sensation that his or her "skin is crawling." Lowering the dosage of the antipsychotic or switching to a second-generation antipsychotic are treatment options. Propranolol in doses of 10 mg two or three times a day is an effective treatment for akathisia.

Neuroleptic malignant syndrome (NMS) is a potentially fatal delirium that develops in some patients in response to antipsychotic agents (Susman 2001). The diagnosis is made on the basis of the triad of symptoms of altered level of consciousness, muscular rigidity (often described as lead-pipe rigidity), and autonomic instability. The autonomic instability includes hyperthermia, tachycardia, labile blood pressure, diaphoresis, incontinence, and occasional dysphagia and bowel obstruction. Associated findings can include elevated creatine phosphokinase (CPK), leukocytosis, and metabolic acidosis. Later complications include rhabdomyolysis and renal failure. The main interventions in NMS are discontinuation of the offending agent and provision of general supportive measures, including cooling, rehydration, intensive nursing care, and anticoagulation. Pharmacological options can include benzodiazepines, bromocriptine (15 mg/day), dantrolene (100-300 mg/day), or amantadine (200 mg/day). ECT also has been used to treat NMS.

The atypical antipsychotic clozapine can cause catastrophic agranulocytosis in up to 1% of patients treated. This usually occurs within 6 weeks to 6 months of initiating therapy with clozapine. A white blood cell count of less than 3,500/mm^3 or a granulocyte count of less than 1,500/mm^3 warrants discontinuation of the medication.

Other signs of impending marrow failure are fever, flulike symptoms, and sore throat. Discontinuation of the clozapine, supportive measures, and treatment of specific infections if identified are the main interventions for agranulocytosis, and in life-threatening cases, growth factors such as filgrastim may be utilized.

Antidepressants

Adverse events associated with tricyclic antidepressants include anticholinergic delirium, cardiac conduction delays, and seizures. Anticholinergic delirium is more common in elderly and impaired individuals and may be potentiated by concomitant anticholinergic medications. Furthermore, the coadministration of an SSRI or other drug known to inhibit the cytochrome P450 2D6 enzyme with a tricyclic antidepressant can cause dramatic increases in tricyclic antidepressant blood levels and resultant delirium. These drugs also can affect cardiac conduction, can lower seizure thresholds, and are lethal in overdose. The principal intervention is to decrease or discontinue the offending agent.

A hypertensive crisis can occur in an individual who is taking monoamine oxidase inhibitors. This usually happens after ingestion of a large dose of tyramine (which can be found in certain food products) or after an interaction with another medication (e.g., meperidine, other antidepressants, sympathomimetic agents). Discontinuation of the monoamine oxidase inhibitor and management of the hypertension are the appropriate treatments.

Serotonin syndrome is a delirium characterized by altered level of consciousness, autonomic instability, and neuromuscular abnormalities including myoclonus, hyperreflexia, nystagmus, akathisia, and muscle rigidity (Martin 1996; Mason *et al.* 2000). Several different drugs, usually administered in combination, can cause this adverse event. Medications reported to provoke serotonin syndrome include SSRIs, tricyclic antidepressants, monoamine oxidase inhibitors, venlafaxine, trazodone, nefazodone, lithium, tryptophan, meperidine, sumatriptan, buspirone, duloxetine, milnacipran, and amphetamines. Discontinuation of the offending agent and general supportive measures are the principal interventions. Unlike in NMS, bromocriptine can worsen the serotonin syndrome. Other drugs useful in treating this condition are benzodiazepines, cyproheptadine, chlorpromazine, methysergide, and propranolol.

Although not a life-threatening emergency, SSRI discontinuation syndrome can be very frightening and distressing to patients. This syndrome develops after abrupt discontinuation of a short-half-life SSRI, with paroxetine and venlafaxine the two most common agents. Symptoms can include dizziness, malaise, nausea, paresthesias, tremor, ataxia, confusion, myoclonus, anxiety, and vivid dreaming. Symptoms usually develop 48 hours after the last dose, peak around day 4-5, and can last as long as 2 weeks. Interventions include reassuring the patient and restarting the medicine, followed by a very gradual taper.

Priapism is a rare but potentially serious adverse event that has been associated with psychotropic medications including trazodone. This physiological condition is usually self-limiting. However, a patient with an erection lasting for more than 4 hours warrants an immediate evaluation and treatment by appropriate medical personnel (Montague *et al.* 2003). Patients should always be warned of this rare but serious potential side effect.

Conclusion

In the modern era, with changes in the mental health care delivery systems and the resultant limitations placed on the utilization of inpatient treatment resources, the emergency psychiatrist will increasingly be called upon to diagnose and initiate definitive treatment of patients with a wide range of psychiatric disorders. Emergency psychiatrists must balance the needs of individual patients with those of the larger community, the health care system, and the third-party payer system, with a focus on delivering care that is both efficacious and cost-effective. This requires a broad knowledge base, incorporating elements of all branches of psychiatry, and consideration of thorough yet expeditious evaluation, diagnosis, and treatment of patients with mental illnesses.

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APPENDIX

of Psychiatric Medications

Robert H. Chew, Pharm.D.
Robert B. MacArthur, Pharm.D., M.S.

		Adult		Pedi
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**
ANTIDEPRESSANTS				
Tricyclic and tetracyclic antidepressants				
Secondary tricyclics				
Desipramine (Norpramin)	MDD	100-200 mg/day (at bedtime or in divided doses)	300	Ages [?] 13 years: 25-100 mg/day (at bedtime or in divided doses)
Nortriptyline (Pamelor)	MDD	75-100 mg/day (once daily or divided tid-qid)	150	Ages 6-12 years: 1-3 mg/kg/day (divided tid-qid
				Ages > 12 years: 30-50 mg/day (once daily

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized
disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d
Mitigation Strategy.

-- = not available; bid = twice daily (or divided into 2 doses); IM = intramuscular; IV = intravenous; PO = oral; prn = as needed; qid = four times daily (or
sublingual; tid = three times daily (or divided into 3 doses).

CD = controlled delivery (extended release); CR = controlled release (extended release); ER = extended release; IR = immediate release; LA = long acting
(extended release); XL, XR = extended release.

Source. Athenahealth Inc.: epocrates(r); Available at: http://online.epocrates.com; Findling RL (ed): *Clinical Manual of Child and Adolescent Psy*
Psychiatric Publishing, 2008; National Institutes of Health, U.S. National Library of Medicine: DailyMed; available at: http://dailymed.nlm.nih.gov; W
available at: http://eanswers.factsandcomparisons.com.

		Adult		
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**
				or divided tid-qid
Protriptyline (Vivactil)	MDD	15-40 mg/day (divided tid-qid)	60	Ages [?] 12 years: 15 mg/day (divided tid)
Tertiary tricyclics				
Amitriptyline (Elavil)	MDD	50-150 mg/day (at bedtime or in divided doses)	300	Ages [?] 12 years: 50-100 mg/day (once daily or in divided doses)
MDD, hospitalized patients	100-200 mg/day (at bedtime or in divided doses)	300		
Clomipramine (Anafranil)	OCD	150-250 mg/day (at bedtime or in divided doses)	250	Ages [?] 10 years: 100-200 mg/day (at bedtime or in divided doses)
Doxepin	Depression and/or anxiety			
	Mild to moderate symptoms	75-150 mg/day (at bedtime or in divided doses)	150	
Severe symptoms	300 mg/day (at bedtime or in divided doses)	300		
Doxepin (Silenor)	Insomnia (sleep maintenance)	3-6 mg at bedtime	6	

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized
disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d
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(extended release); XL, XR = extended release.

Source. Athenahealth Inc.: epocrates(r); Available at: http://online.epocrates.com; Findling RL (ed): *Clinical Manual of Child and Adolescent Psy*
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available at: http://eanswers.factsandcomparisons.com.

		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
Imipramine (Tofranil)	MDD	50-150 mg/day (at bedtime or in divided doses)	200	Ages [?] 13 years: 30-40 mg/day (at bedtime or in divided doses)	1
	MDD, hospitalized patients	250-300 mg/day (in divided doses)	300		
	Nocturnal enuresis			Ages 6-12 years: 10-50 mg at bedtime	5
				Ages > 12 years: 10-75 mg at bedtime	75
Trimipramine (Surmontil)	MDD	50-150 mg/day (at bedtime or in divided doses)	200	Ages [?] 13 years: 50-100 mg/day (at bedtime or in divided doses)	1
	MDD, hospitalized patients	250-300 mg/day (at bedtime or in divided doses)	300		
Tetracyclics					
Amoxapine	MDD	200-300 mg/day (at bedtime or in divided doses)	400		
	MDD, hospitalized patients	200-300 mg/day (at bedtime or	600		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**
		in divided doses)		
Maprotiline	MDD	75-150 mg/day (at bedtime or in divided doses)	150	
	MDD, hospitalized patients	150-225 mg/day (at bedtime or in divided doses)	225	
Selective serotonin reuptake inhibitor (SSRI) antidepressants				
Citalopram (Celexa)	MDD	20-40 mg/day	40	
Escitalopram (Lexapro)	MDD	10-20 mg/day	20	Ages 12-17 years: 10-20 mg/day
	GAD	10-20 mg/day	20	
Fluoxetine (Prozac)	MDD	20-80 mg/day in morning or divided bid; or 90 mg weekly$^+$	80	Ages [?] 8 years: 10-20 mg/day in morning
	OCD	20-60 mg/day in morning or divided bid	80	Ages [?] 7 years: 20-60 mg/day in morning or divided bid
	Panic disorder	20-60 mg/day	60	
	Bulimia nervosa	20-60 mg/day	60	
Fluoxetine (Sarafem)	PMDD	20-60 mg/day$^+$	80	

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	Approved indications	Usual dosage	Maximum (mg/day)	Usual dosage	
Fluvoxamine	OCD	100-300 mg/day (divided bid)	300	Ages 8-17 years: 50-200 mg/day (divided bid)	2
				Ages > 17 years: 100-300 mg/day (divided bid)	3
Fluvoxamine extended-release (Luvox CR)	OCD	100-300 mg/day at bedtime	300		
Paroxetine (Paxil)	MDD	20-50 mg/day in morning	50		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	**I (**
Paroxetine extended-release (Paxil CR)		CR: 25-62.5 mg/day	62.5		
	GAD	20-50 mg/day	50		
	Social anxiety disorder	20-60 mg/day	60	Ages 8-17 years:* 10-60 mg/day in morning	6
		CR: 12.5-37.5 mg/day	37.5		
	Panic disorder	40 mg/day in morning	60		
		CR: 12.5-75 mg/day in morning	75		
	OCD	20-60 mg/day in morning	60	Ages 7-17 years:* 10-60 mg/day in morning	6
	PTSD	20-50 mg/day in morning	50		
PMDD	CR: 12.5-25 mg/day in morning+	25			+
Paroxetine mesylate (Brisdelle)+	Moderate to severe vasomotor symptoms associated with menopause	7.5 mg/day at bedtime	--		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized
disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d
Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	**I (**
Sertraline (Zoloft)	MDD	50-200 mg/day in morning	200	Ages [?] 6 years:* 25-200 mg/day in morning	2
	Social anxiety disorder	50-200 mg/day	200		
	Panic disorder	50-200 mg/day in morning	200		
	OCD	50-200 mg/day in morning	200	Ages 6-12 years: 25-200 mg/day	2
				Ages 13-17 years: 50-200 mg/day	2
	PTSD	50-200 mg/day in morning	200		
PMDD	50-200 mg/day in morning^{+}	150			+
Serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants					
Desvenlafaxine (Pristiq)	MDD	50 mg/day	50		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult			Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**		**Usual dosage**	
Duloxetine delayed-release (Cymbalta;$^{+}$ Drizalma Sprinkle^{++})	MDD	40-60 mg/day (once daily or divided bid)	120			
	GAD	60 mg/day	120		Ages 7-17 years: 30-60 mg/day	1
	Diabetic neuropathic pain	60 mg/day	60			
	Musculoskeletal pain	60 mg/day	60			
Fibromyalgia	60 mg/day	60		Ages 13-17 years:$^{+}$ 60 mg/day	60	$^{+}$
Levomilnacipran (Fetzima)	MDD	40-120 mg/day	120			
Milnacipran (Savella)	Fibromyalgia	100 mg/day (divided bid)	200			
Venlafaxine	MDD	75-225 mg/day	225			
Venlafaxine extended-release (Effexor ER)	MDD	75-225 mg/day	225			
	GAD	75-225 mg/day	225			
	Social anxiety disorder	75 mg/day	75			
	Panic disorder	75-225 mg/day	225			

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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	Adult			Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
Venlafaxine besylate extended-release tablets (112.5 mg)$^+$	MDD GAD	112.5 mg once daily with food	225		
Norepinephrine-dopamine reuptake inhibitor (NDRI) antidepressant (putativeSS)					
Bupropion immediate-release	MDD	300 mg/day (divided tid)	150 mg/dose; 450 mg/day		
	ADHD*	300 mg/day (divided tid)	$^+$	Ages [?] 6 years: 1.4-6.0 mg/kg/day (divided bid)	$^+$
			$^+$Maximum dosing (adult and pediatric) for bupropion IR: 150 mg/dose; 450 mg/day		
Bupropion sustained-release (Wellbutrin SR)	MDD	SR: 300 mg/day (divided bid)	400		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	**I (**
	ADHD*	SR: 300 mg/day (divided bid)	400	Ages [?] 12 years: 3-6 mg/kg/day (divided bid)	4
Bupropion extended-release					
Bupropion XL	MDD, seasonal affective disorder	300 mg/day in morning	450		
	ADHD*	300 mg/day in morning	300	Ages [?] 12 years: 3-6 mg/kg/day in morning	4
Aplenzin	MDD, seasonal affective disorder	348 mg/day in morning	522		
Multimodal serotonin antagonist antidepressants					
Nefazodone++	MDD	300-600 mg/day (divided bid)	600		
	Depression	Refer to manufacturer's full prescribing information for dosing guidelines and titration schedule.	600		
Trazodone	MDD	150-300 mg/day (divided bid-tid)	400		
	Insomnia*	25-100 mg/day at bedtime	200		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**
Trazodone extended-release$^+$	MDD	150-375 mg/day at bedtime	375	
Serotonin-modulating antidepressants				
Vilazodone (Viibryd)	MDD	20-40 mg/day	40	
Vortioxetine (Trintellix)	MDD	20 mg/day	20$^+$	
Noradrenergic-specific serotonin antidepressant (NaSSA)				
Mirtazapine (Remeron)	MDD	15-45 mg/day at bedtime	45	
Selective serotonin 1A receptor partial agonist antidepressant				
Gepirone extended-release (Exxua)	MDD	Start with 18.2 mg/day. Dosage may be increased to 36.3 mg/day on day 4, and may be further titrated to 54.5 mg/day after day 7 and to 72.6 mg/day after an additional week.	72.6	

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
Neuroactive steroid GABA-A receptor positive allosteric modulator (PAM) antidepressants					
Brexanolone injection (Zulresso)++	PPD in patients ages 15 years and older	Administered as a continuous IV infusion over 60 hours (2.5 days).$^+$ Refer to manufacturer's full prescribing information for recommended dosing.	--		
Zuranolone capsules (Zurzuvae)	PPD	Refer to manufacturer's full prescribing information for recommended dosing.	--		
Monoamine oxidase inhibitor (MAOI) antidepressants					
Isocarboxazid (Marplan)	MDD and atypical depression	40-60 mg/day (divided bid-qid)	60		
Phenelzine (Nardil)	MDD and atypical depression	40-60 mg/day in divided doses$^+$	90		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
Selegiline transdermal patch (Emsam)	MDD	6-12 mg patch per 24 hours	12		
Selegiline hydrochloride (Zelapar ODT [orally disintegrating tablets])	Management of patients with Parkinson's disease being treated with levodopa/carbidopa	1.25 mg given once daily for at least 6 weeks. After 6 weeks, daily dosage may be escalated up to 2.5 mg.	2.5		
Tranylcypromine (Parnate)	MDD and atypical depression	30 mg/day in divided doses	60		
NMDA receptor antagonist antidepressants					
Dextromethorphan hydrobromide/bupropion hydrochloride extended-release tablets (Auvelity)	MDD	Start with 1 tablet (45 mg/105 mg) daily taken in the morning. After 3 days, increase to maximum recommended dosage of 1 tablet taken twice daily, separated by at least 8 hours.	Do not exceed two 1-tablet doses taken within the same day.		
Esketamine nasal spray (Spravato)++	Treatment-resistant depression	Refer to manufacturer's full prescribing	--		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	Approved indications	Usual dosage	Maximum (mg/day)	Usual dosage	I (
		information for recommended dosing.+			
	Depressive symptoms with acute suicidal ideation or behavior in patients with MDD	--			+
Ketamine	Relief of acute depression with suicidal ideation*	0.5 mg/kg IV infusion over 40 minutes	--		
ANXIOLYTICS					
Benzodiazepine GABA-A receptor PAMs					
Alprazolam (Xanax)	GAD	0.25-0.5 mg tid	4		
	Panic disorder	1.5-9 mg/day (divided tid)	10		
Alprazolam extended-release (Xanax XR)	GAD	3-6 mg/day	6		
Chlordiazepoxide	GAD, mild to moderate	5-10 mg tid-qid	+	Ages [?] 6 years: 5-10 mg bid-tid	+
	GAD, severe	20-25 mg tid-qid	+		
	Acute alcohol withdrawal	50-100 mg prn	300		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized
disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d
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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
Clonazepam (Klonopin)	Panic disorder	1-4 mg/day (divided bid)	4		
Clorazepate	GAD	15-30 mg/day (at bedtime or divided bid)	60		
	Acute alcohol withdrawal	Refer to manufacturer's full prescribing information for recommended dosing guidelines and titration schedules.	--		
Diazepam (Valium)	GAD	2-10 mg bid-qid	40		
	Acute alcohol withdrawal	10 mg tid-qid for first 24 hours; then 5 mg tid-qid prn	-- 730		
Lorazepam (Ativan)	GAD	2-6 mg/day (divided bid-tid)	10		
	Anxiety-associated insomnia	2-4 mg at bedtime	4		
Lorazepam injection (Ativan Injection)	Acute agitation*	0.5-1 mg IM prn every 30-60 minutes	--		
Lorazepam extended-release capsules (Loreev XR)	Anxiety disorders in adults who are receiving stable, evenly divided, three-times-daily dosing with	Refer to manufacturer's full prescribing information for	--		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	Approved indications	Usual dosage	Maximum (mg/day)	Usual dosage	
	lorazepam tablets	recommended dosing.			
Oxazepam	GAD	10-30 mg tid-qid	120		
	Acute alcohol withdrawal	15-30 mg tid-qid	--		
Serotonin-1A receptor partial agonist					
Buspirone	GAD	20-30 mg/day (divided bid-tid)	60		
AGENTS FOR TREATMENT OF INSOMNIA					
Benzodiazepine GABA-A receptor PAMs					
Estazolam	Insomnia (sleep onset/maintenance; nocturnal or early-morning awakening)	1-2 mg at bedtime	2		
Flurazepam (Dalmane)	Insomnia (sleep onset/maintenance)	15-30 mg at bedtime	30		
Quazepam (Doral)	Insomnia (sleep onset; nocturnal or early-morning awakening)	7.5-15 mg at bedtime	15		
Temazepam (Restoril)	Insomnia (sleep onset/maintenance)	7.5-30 mg at bedtime	30		
Triazolam (Halcion)	Insomnia (sleep onset/maintenance)	0.125-0.5 mg at bedtime	0.5; 0.25 in elderly		
Nonbenzodiazepine GABA-A receptor PAMs					
Eszopiclone (Lunesta)	Insomnia (sleep onset/maintenance)	1-3 mg at bedtime	3		
Zaleplon (Sonata)	Insomnia (middle-of-night	10-20 mg at bedtime	20		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
	awakening)				
Zolpidem (Ambien)	Insomnia (sleep onset)	5-10 mg at bedtime	10		
Zolpidem extended-release (Ambien CR)	Insomnia (sleep onset/maintenance)	6.5-12.5 mg	12.5		
Zolpidem sublingual (SL) (Intermezzo)	Insomnia (sleep initiation)[+]	Women: 1.75 mg prn Men: 3.5 mg prn	Once per night		
Melatonin receptor agonists					
Ramelteon (Rozerem)	Insomnia (sleep onset)	8 mg at bedtime	8		
Tasimelteon (Hetlioz)	Non-24-hour sleep-wake disorder	20 mg at bedtime	20		
	Nighttime sleep disturbance in Smith-Magenis syndrome (SMS) in patients ages 16 years and older	20 mg taken 1 hour before bedtime	20	20 mg taken 1 hour before bedtime	2
	Nighttime sleep disturbance in SMS in pediatric patients ages 3-15 years			20 mg taken 1 hour before bedtime; if weight less than 28 kg, 0.7 mg/kg taken 1 hour before bedtime	(
Orexin receptor antagonists					

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	**I (**
Daridorexant (Quviviq)	Insomnia (sleep onset/maintenance)	25-50 mg at bedtime	50		
Lemborexant (Dayvigo)	Insomnia (sleep onset/maintenance)	5-10 mg once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening	10		
Suvorexant (Belsomra)	Insomnia (sleep onset/maintenance)	10-20 mg at bedtime	20		
ANTIPSYCHOTICS					
First-generation (typical) antipsychotics					
Chlorpromazine	Psychotic disorders	200-600 mg/day (divided tid-qid)	1,000		
	Acute manic states, hospitalized patients	200-800 mg/day (divided tid-qid)	2,000		
Chlorpromazine injection	Acute agitation, hospitalized patients	25 mg IM, repeat 25-50 mg in 1 hour; up to 400 mg IM every 4-6 hours prn	--		
Fluphenazine	Psychotic disorders	2.5-10 mg/day (divided tid-qid)	40		

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		Adult		Pedi
Medication	Approved indications	Usual dosage	Maximum (mg/day)	Usual dosage
Fluphenazine hydrochloride injection	Acute agitation	2.5-10 mg/day IM every 6-8 hours prn	10	
Fluphenazine decanoate injection	Management of psychotic disorders and schizophrenia	25-50 mg IM every 3 weeks^{+}	--	
Haloperidol	Psychotic disorders	0.5-5 mg bid-tid	100	Ages 3-12 years: 0.05-0.15 mg/ kg/day
				Ages > 12 years: 0.5-5 mg bid-tid
	Tourette's disorder	0.5-5 mg bid-tid	100	Ages 3-12 years: 0.05-0.075 mg/ kg/day
				Ages > 12 years: 0.5-5 mg bid-tid
	Behavioral disorders, severe			Ages 3-12 years: 0.05-0.075 mg/ kg/day
				Ages > 12 years: 0.5-5 mg bid-tid

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized
disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d
Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
Haloperidol lactate injection (Haldol Injection)	Acute psychosis	2-10 mg IM every 4-8 hours prn	20		
Haloperidol decanoate injection (Haldol Decanoate)	Management of psychotic disorders and schizophrenia	50-200 mg IM every month	--		
Loxapine (Loxitane)	Psychotic disorders	60-100 mg/day in divided doses	250		
Loxapine inhalation (Adasuave)++	Acute agitation	10 mg/day^{+}	10		
Perphenazine	Psychotic disorders	4-8 mg tid	24		
	Psychotic disorders, hospitalized patients	8-16 mg bid-qid	64		
Pimozide (Orap)	Tourette's disorder	2-10 mg/day	10	Ages [?] 12 years: 0.05-0.2 mg/ kg/day	
Thioridazine	Psychotic disorders	200-800 mg/day (divided bid-qid)	800		
Thiothixene	Psychotic disorders	20-30 mg/day in divided doses	60		
Trifluoperazine	Psychotic disorders	15-20 mg/day (once daily or	40	Ages 6-12 years: 1	1

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	**I (**
		divided bid)		mg/day (once daily or divided bid)	
				Ages [?] 13 years: 15-20 mg/day (once daily or divided bid)	4
	Nonpsychotic anxiety	1-2 mg bid	6		
Second-generation (atypical) antipsychotics					
Aripiprazole (Abilify)	Schizophrenia	10-15 mg/day	30	Ages 13-17 years: 10 mg/day	3
	Bipolar I disorder	10-15 mg/day	30	Ages 10-17 years: 10 mg/day	3
	MDD, as adjunctive therapy with antidepressants	2-15 mg/day	15		
	Tourette's disorder			Ages 6-18 years, < 50 kg: 5 mg/day	1
				Ages 6-18 years, [?] 50 kg: 10 mg/day	2

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	**I (**
	Irritability associated with autism spectrum disorder			Ages 6-17 years: 5-10 mg/day	1
Aripiprazole long-acting IM injection (Abilify Maintena)	Schizophrenia	300-400 IM every month	--		
Aripiprazole lauroxil long-acting IM injection (Aristada)	Schizophrenia	441-882 IM every 4-6 weeks	--		
Asenapine SL (Saphris)	Schizophrenia	10-20 mg/day SL (divided bid)	20		
	Bipolar I disorder, monotherapy	10-20 mg/day SL (divided bid)	20	Ages 10-17 years: 5-10 mg/day SL (divided bid)	2
	Bipolar I disorder, as adjunctive therapy with lithium or valproate	10 mg/day SL (divided bid)	20		
Asenapine transdermal system (Secuado)	Schizophrenia	One 3.8 mg patch every 24 hours; may increase dosage to 5.7 mg/24 hours or 7.6 mg/24 hours after 1 week	7.6		
Brexpiprazole (Rexulti)	Schizophrenia	2-4 mg/day	4	Ages 13-17 years: 2-4 mg/day	4
	MDD, as adjunctive	2 mg/day	3		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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	Adult			Pedi	
Medication	Approved indications	Usual dosage	Maximum (mg/day)	Usual dosage	
	therapy with antidepressants				
	Agitation associated with dementia due to Alzheimer's disease++	2 mg/day	3		
Cariprazine (Vraylar)	Schizophrenia	1.5-6 mg/day	6		
	Bipolar I disorder	3-6 mg/day	6		
	Bipolar depression	1.5-3 mg/day	3		
	MDD, as adjunctive therapy with antidepressants	1.5-3 mg/day	3		
Clozapine (Clozaril)++	Schizophrenia, refractory	150-300 mg bid	900		
	Schizophrenia with high suicide risk	150-300 mg bid	900		
Iloperidone (Fanapt)	Schizophrenia	6-12 mg bid	24		

Lumateperone (Caplyta)	Schizophrenia	42 mg/day	42		
	Bipolar depression, as monotherapy	42 mg/day	42		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
	or as adjunctive therapy with lithium or valproate				
Lurasidone (Latuda)	Schizophrenia	40-160 mg/day	160	Ages 10-17 years: 40-80 mg/day	8
	Bipolar depression, as adjunctive therapy with lithium or valproate	20-120 mg/day	120		
	Bipolar depression, as monotherapy	20-120 mg/day	120	Ages 10-17 years: 20-80 mg/day	8
Olanzapine (Zyprexa)	Schizophrenia	10-20 mg/day	20	Ages [?] 13 years: 10 mg/day	2
	Bipolar I disorder	5-20 mg/day	20	Ages [?] 13 years: 10 mg/day	2
Olanzapine IM injection (Zyprexa Intramuscular)	Acute agitation	10 mg IM; may repeat after 2 hours one time; repeat prn 4 hours after second dose	30		
Olanzapine long-acting IM injection (Zyprexa Relprevv)++	Schizophrenia	Refer to manufacturer's recommended dosing guidelines and titration schedules.			
Olanzapine/fluoxetine (Symbyax)	Bipolar I disorder, acute depressive	6 mg/25 mg/day-12	12/50	Ages 10-17 years: 3	1

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**
	episodes	mg/50 mg/ day		mg/25 mg/day
	Treatment-resistant depression	6 mg/25 mg/day	12/50	
Olanzapine/samidorphan (Lybalvi)	Schizophrenia	Starting: 5 mg/10 mg or 10 mg/10 mg	20/10	
		Recommended: 10 mg/10 mg, or 15 mg/10 mg, or 20 mg/10 mg		
	Bipolar I disorder, manic or mixed episodes, as monotherapy	Starting: 10 mg/10 mg or 15 mg/10 mg	20/10	
		Recommended: 5 mg/10 mg, or 10 mg/10 mg, or 15 mg/10 mg, or 20 mg/10 mg		
	Bipolar I disorder, as adjunctive therapy with lithium or valproate	Starting: 10 mg/10 mg	20/10	
		Recommended: 10 mg/10 mg, or 15 mg/10 mg, or 20 mg/10 mg		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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	Adult				Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**		**Usual dosage**	**I (**
Paliperidone (Invega)	Schizophrenia	6 mg/day	12		Ages 12-17 years: 3 mg/day	1
Paliperidone palmitate long-acting IM injection	Schizoaffective disorder	$^{+}$		--		
Invega Sustenna (IM monthly injection)		$^{+}$		--		
Invega Trinza (IM injection every 3 months)	Patients who have been adequately treated with once-a-month Invega Sustenna for at least 4 months	Depends on previous Invega Sustenna once-a-month dosage^{+}		--		
Invega Hafyera (IM injection every 6 months)	Patients who have been adequately treated with either 1) once-a-month Invega Sustenna for at least 4 months or 2) every-3-month Invega Trinza for at least one 3-month cycle	Depends on previous Invega Sustenna once-a-month dosage^{+}		--		
Pimavanserin (Nuplazid)	Hallucinations and delusions associated with Parkinson's disease	34 mg taken orally as two 17-mg tablets once daily, without titration	34	742		
Quetiapine (Seroquel)	Schizophrenia	150-750 mg/day (divided bid-tid)	750		Ages 13-17 years: 400-800 mg/day	8

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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	Adult			Pedi	
Medication	Approved indications	Usual dosage	Maximum (mg/day)	Usual dosage	
				(divided bid-tid)	
	Bipolar I disorder, acute manic/ mixed episodes	400-800 mg/day (divided bid)	800	Ages 10-17 years: 400-600 mg/day (divided bid-tid)	6
	Bipolar I disorder, depressive episodes	300 mg/day at bedtime	300		
Quetiapine extended-release (Seroquel XR)	Schizophrenia	400-800 mg/day	800	Ages 13-17 years): 400-800 mg/day	8
	Bipolar I disorder, acute manic/ mixed episodes	400-800 mg bid	800	Ages 10-17 years): 400-600 mg/day	6
	Bipolar I disorder, depressive episodes	300 mg/day at bedtime	300		
	MDD, as adjunctive therapy with antidepressants	150-300 mg/day	300		
Risperidone (Risperdal)	Schizophrenia	4-8 mg/day (once daily or divided bid)	16	Ages 13-17 years: 1-6 mg/day (once daily or divided bid)	6
	Bipolar I disorder, acute manic/ mixed episodes	1-6 mg/day (once daily or divided bid)	6	Ages 10-17 years: 1-2.5 mg/day (once daily or divided bid)	6

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
	Irritability associated with autism spectrum disorder			Ages 5-17 years, weight < 20 kg: 0.5 mg/day (once daily or divided bid)$^{+}$	3
				Ages 5-17 years, weight [?] 20 kg: 1 mg/day (once daily or divided bid)$^{+}$	3
Risperidone long-acting IM injection (Risperdal Consta)	Schizophrenia	25-50 mg IM every 2 weeks	--		
	Bipolar I disorder	25-50 mg IM every 2 weeks	--		
Ziprasidone (Geodon)	Schizophrenia	20 mg bid	160		
	Bipolar I disorder	80-160 mg/day (divided bid)	160		
Ziprasidone IM injection (Geodon Injection)	Acute agitation	10 mg IM every 2 hours prn or 20 mg IM every 4 hours prn	--		
MOOD STABILIZERS					
Lithium					
Lithium carbonate	Bipolar disorder	900-1,200 mg/day (divided tid-qid)$^{+}$	2,400	Ages [?] 6 years, weight < 30 kg: 15-40 mg/kg/day	6

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**
				(divided tid-qid)$^{+}$
				Ages [?] 6 years, weight [?] 30 kg: 15-40 mg/kg/day (divided tid-qid)$^{+}$
Lithium extended-release (Lithobid)	Bipolar disorder	900-1,800 mg/day (divided bid-tid)	1,800	Ages [?] 6 years, weight < 30 kg: 15-40 mg/kg/day (divided tid-qid)
				Ages [?] 6 years, weight [?] 30 kg: 15-40 mg/kg/day (divided tid-qid)
Anticonvulsants				
Carbamazepine (Tegretol)	Bipolar I disorder*	800-1,200 mg/day (divided bid-qid)	1,600	
Carbamazepine extended-release (Equetro,$^{+}$ Tegretol XR)	Bipolar I disorder	400-600 mg bid	1,600	

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disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d
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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	**I (**
Gabapentin (Neurontin)	Postherpetic neuralgia	300-600 mg tid	1,800		
	Neuropathic pain*	300-1,200 mg tid	3,600		
	Bipolar I disorder*	600-3,600 mg/day (divided tid)	3,600		
	GAD*	600-3,600 mg/day (divided tid)	3,600		
Lamotrigine (Lamictal, Lamictal XR)	Bipolar I disorder				
	Monotherapy^{+}	200 mg/day	200		
	With valproate^{+}	100 mg/day	100		
	With enzyme inducers (e.g., carbamazepine)$^{+}$	200 mg bid	400		
Bipolar depression*	50-200 mg/day	200			*
Oxcarbazepine (Trileptal)	Bipolar I disorder*	1,200-2,400 mg/ day (once	2,400		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
		daily or divided bid)			
Oxcarbazepine extended-release (Oxtellar XR) 746					
Pregabalin (Lyrica)	GAD*	300 mg bid	600		
	Fibromyalgia	150-225 mg bid	450		
	Diabetic neuropathy	100 mg tid	300		
	Neuropathic pain associated with spinal cord injury	300 mg/day within 1 week	600		
	Postherpetic neuralgia	300 mg/day within 1 week	600		
Pregabalin extended-release (Lyrica CR)	Pain--diabetic peripheral neuropathy	165 mg/day	330		
	Pain--postherpetic neuralgia	165 mg/day	660		
Topiramate (Topamax)	Bulimia nervosa*	300-400 mg/day (divided bid)	400		
	Depressive disorders, as adjunctive therapy with antidepressants*	100-200 mg/day (divided bid)	--		
	Alcohol use disorder*	300 mg/day in divided doses	300		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		**Pedi**	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	**I (**
Valproate, divalproex sodium (Depakote, Depakote ER)	Bipolar I disorder, manic episodes Extended-release tablets (Depakote ER): Take once daily.	15-20 mg/kg/day Rapid oral loading:+ 20-30 mg/kg/day Delayed-release tablets (Depakote): Take in divided doses.	60 mg/kg/ day		
PSYCHOSTIMULANTS FOR TREATMENT OF ADHD AND NARCOLEPSY					
Amphetamine formulations					
Amphetamine extended-release (Dyanavel XR)	ADHD in patients ages 6 years and older+	Starting dose is 2.5 mg or 5 mg once daily taken in the morning. Increase ***in increments of 2.5-10 mg/day every 4-7 days.	20	Starting dose is 2.5 mg or 5 mg once daily taken in the morning. Increase in increments of 2.5-10 mg/day every 4-7 days.	2
Amphetamine/dextroamphetamine (Adderall)	ADHD	5-40 mg/day (once daily or divided bid)	40	Ages 3-5 years: 2.5-40 mg/day (once daily or divided bid)	4
			Ages [?] 6 years:	40	

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult			Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**		**Usual dosage**	**I (**
				5-40 mg/day (once daily or divided bid)	748	
	Narcolepsy^{+}	5-60 mg/day in divided doses	60		5-60 mg/day in divided doses	6
Amphetamine/dextroamphetamine extended-release (Adderall XR)	ADHD	20 mg/day in morning	60		Ages 6-12 years: 10 mg/day in morning	3
					Ages 13-17 years: 10-20 mg/day in morning	4
Dextroamphetamine (Dexedrine)	ADHD				Ages [?] 6 years: 5-40 mg/day (once daily or divided bid)	4
	Narcolepsy	5-60 mg/day (once daily or divided bid)	60		Ages [?] 12 years: 5-60 mg/day (once daily or divided bid)	6
Methamphetamine (Desoxyn)	ADHD	20-25 mg/day (once daily or divided bid)	25		Ages [?] 6 years: 20-25 mg/day (once daily	2

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized
disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d
Mitigation Strategy.

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	Adult				**Pedi**	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**		**Usual dosage**	**I (**
					or divided bid)	
Lisdexamfetamine (Vyvanse)	ADHD	30-70 mg/day in morning	70		Ages [?] 6 years: 30-70 mg/day in morning	7
	Binge-eating disorder	50-70 mg/day in morning	70			
Methylphenidate formulations						
Dexmethylphenidate (Focalin)	ADHD	5-10 mg/day (divided bid)	20		Ages [?] 6 years: 5-20 mg/day (divided bid)	2
Dexmethylphenidate extended-release (Focalin XR)		20-40 mg/day in morning	40		Ages [?] 6 years: 10-30 mg/day in morning	3
Methylphenidate						
Short-acting^{+}						
Ritalin, Methylin	ADHD	20-30 mg/day (divided bid-tid)	60		Ages [?] 6 years: 15-30 mg/day (divided bid-tid)	6
	Narcolepsy	20-30 mg/day (divided bid-tid)	60	750		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**
Intermediate-acting^{+}				
Metadate ER	ADHD	20-40 mg/day (once daily or divided bid)	60	Ages [?] 6 years: 20 mg/day (once daily or divided bid)
	Narcolepsy	20-30 mg/day (once daily or divided bid)	60	
Long-acting^{+}	ADHD			
Aptensio XR		10-60 mg/day in morning	60	Ages [?] 6 years: 10-60 mg/day in morning
Concerta		18-72 mg/day in morning	72	Ages 6-12 years: 18-54 mg/day in morning
				Ages 13-17 years: 18-72 mg/day in morning
Daytrana Transdermal System		10-30 mg patch per day^{+}	30	Ages [?] 6 years: 10-30 mg patch per day
Metadate CD, Quillivant XR, Ritalin LA		20-60 mg/day in morning	60	Ages [?] 6 years: 20-60 mg/day in morning
Other psychostimulants				

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult			Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**		**Usual dosage**	**I (**
Armodafinil (Nuvigil)	Narcolepsy Sleep apnea	150-250 mg/day in morning	250			
Modafinil (Provigil)	Narcolepsy Sleep apnea	200 mg/day in morning	400			
Calcium, magnesium, potassium, and sodium oxybates (Xywav)++	Idiopathic hypersomnia	Refer to manufacturer's full prescribing information for once-nightly and twice-nightly dosing guidelines.	6-9 g			
	Narcolepsy	9 g		Ages [?] 7 years: dosage based on body weight	Based on body weight^{+}	+
NONPSYCHOSTIMULANTS FOR TREATMENT OF ADHD						
Selective norepinephrine reuptake inhibitors						
Atomoxetine (Strattera)	ADHD	80-100 mg/day (divided bid)	100		Ages [?] 6 years, weight < 70 kg: 1.2 mg/kg/day (divided bid)	1
					Ages [?] 6 years, weight [?] 70 kg: 80 mg/day	1

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	Approved indications	Usual dosage	Maximum (mg/day)	Usual dosage	M (
				(divided bid)	
Viloxazine extended-release (Qelbree)	ADHD	200 mg/day	600	Ages [?] 6 years: 100 mg/day	4
Alpha-2 adrenergic receptor agonists					
Clonidine extended-release (Kapvay)	ADHD			Ages [?] 6 years: 0.2-0.4 mg/day (divided bid)	0
Guanfacine extended-release (Intuniv)	ADHD			Ages 6-17 years: 0.05-0.12 mg/kg/day (1-7 mg/day)	+
AGENTS FOR TREATMENT OF COGNITIVE DISORDERS					
Acetylcholinesterase inhibitors					
Donepezil (Aricept)	Alzheimer's disease, mild to moderate	5-10 mg/day	10		
	Alzheimer's disease, moderate to severe	10-23 mg/day	23		
Galantamine (Razadyne)	Alzheimer's disease, mild to moderate	8-12 mg bid	24		
Galantamine extended-release (Razadyne ER)	Alzheimer's disease, mild to moderate	16-24 mg/day	24		
Rivastigmine (Exelon)	Alzheimer's disease, mild to severe	3-6 mg bid	12		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
	Parkinson's disease dementia	1.5-6 mg bid	12		
Rivastigmine topical patch (Exelon Transdermal)	Alzheimer's disease, mild to severe	9.5-13.3 mg patch per 24 hours	13.3		
	Parkinson's disease dementia	9.5-13.3 mg patch per 24 hours	13.3		
NMDA receptor antagonist					
Memantine (Namenda)	Alzheimer's disease, moderate to severe	10 mg bid	20		
Memantine extended-release (Namenda XR)	Alzheimer's disease, moderate to severe	28 mg/day	28		
Memantine/donepezil (Namzaric)	Alzheimer's disease, moderate to severe	28 mg/10 mg/day+	28/10		
Monoclonal antibodies directed against aggregated forms of beta amyloid					
Aducanumab (Aduhelm) IV injection++	Alzheimer's disease, patients with mild cognitive	Refer to manufacturer's full prescribing	--		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	Approved indications	Usual dosage	Maximum (mg/day)	Usual dosage	
	impairment (confirm presence of amyloid beta pathology prior to initiating treatment)	information for administration guidelines and titration schedules.			
Lecanemab (Leqembi) IV injection++					
AGENTS FOR TREATMENT OF MEDICATION-INDUCED MOVEMENT DISORDERS (EPS)					
Dopaminergic					
Amantadine	Medication-induced EPS	100 mg bid	300		
Amantadine extended-release (Gocovri)	Medication-induced EPS	137-274 mg once daily at bedtime	274		
Anticholinergics					
Benztropine (Cogentin)	Medication-induced EPS	1-2 mg PO/IM bid-tid	6	Ages [?] 3 years:* 0.02-0.05 mg/kg/day PO/IM (once daily or bid)	+
Benztropine mesylate injection (Cogentin Injection)	Acute dystonic reaction	2 mg IM; repeat once after 30 minutes prn	+		
Trihexyphenidyl	Medication-induced EPS	5-15 mg/day (divided tid-qid)	15		
Antihistaminic					
Diphenhydramine (Benadryl)	Medication-induced EPS	25-50 mg PO/IM every 6-8 hours prn	400	Ages < 12 years: 1-2 mg/kg	5

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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	Adult			Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	**I (**
				PO/IM every 6-8 hours prn	
				Ages [?] 12 years: 25-50 mg PO/IM every 6-8 hours prn	1
	Acute dystonic reaction*	50-100 mg IM/IV; repeat after 20-30 minutes prn	100 mg/dose	Ages [?] 6 years: 1-2 mg/kg/dose IM/IV; repeat after 20-30 minutes prn	5
Beta-adrenergic receptor antagonist					
Propranolol (Inderal)	Medication-induced akathisia*	20-120 mg/day (divided tid-qid)	120		
Vesicular monoamine transporter 2 (VMAT2) inhibitors					
Deutetrabenazine (Austedo)	Chorea associated with Huntington's disease Tardive dyskinesia	6 mg once daily Gradually increase by 6 mg/day at weekly intervals. For total daily dosage of 12 mg or greater, administer as two divided doses	48		
Valbenazine (Ingrezza)	Tardive dyskinesia Chorea associated with Huntington's disease	40 mg once daily After 1 week, increase to recommended	80		

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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		Adult		Pedi	
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**	
		dosage of 80 mg once daily			
AGENTS FOR TREATMENT OF SUBSTANCE USE DISORDERS					
Acamprosate	Alcohol abstinence, maintenance	666 mg tid	+		
Bupropion sustained-release (Zyban)	Smoking cessation	150 mg bid	300		
Disulfiram (Antabuse)	Alcohol abstinence	125-500 mg/day in morning	500		
Lofexidine (Lucemyra)	Opioid withdrawal symptoms	Three 0.18 mg tablets taken orally 4 times daily at 5-to 6-hour intervals. Treatment may be continued for up to 14 days with dosing guided by symptoms.	2.88 (sixteen 0.18-mg tablets)		
Naltrexone	Alcohol dependence	50 mg/day	+		
	Opioid dependence	Give 25 mg; if no withdrawal symptoms, start 50 mg/day	+		

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		Adult		Pedi
Medication	**Approved indications**	**Usual dosage**	**Maximum (mg/day)**	**Usual dosage**
Naltrexone IM injection (Vivitrol)	Alcohol dependence	380 mg IM every 4 weeks+	--	
	Opioid dependence	380 mg IM every 4 weeks+	--	
Varenicline (Chantix)	Smoking cessation	Requires dosage titration+	0.5 mg twice daily	

Note. ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6 enzyme; EPS = extrapyramidal side effects; GAD = generalized disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PPD = postpartum depression; PTSD = posttraumatic stress d Mitigation Strategy.

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